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PATENT- OG VAREMÆRKESTYRELSEN

AMINOALKOXY-FUNCTIONAL CHALCONES

FIELD OF THE INVENTION

The present invention relates to a novel class of chalcone derivatives and analogues and to their use as pharmaceutically active agents, in particular against bacterial and parasitic infections.

Furthermore, the invention relates to a method of predicting whether a chemical compound has a potential inhibitory effect against an organism selected from *Helicobacter pylori* and *Plasmodium falciparum*. The prediction is based on the ability of the chemical compound to act as an inhibitior of the enzyme dihydroorotate dehydrogenase which is involved in the synthesis of pyrimidine in prokaryotic as well as eukaryotic cells such as bacteria, parasites, fungi, helminths and any type of mammalian cells such as human cells.

BACKGROUND OF THE INVENTION

Chalcones, e.g., for use against parasitic infections are known from earlier patent applications assigned to the applicant, e.g. WO 93/17671 and WO 99/00114.

The bioavailability for several of the known chalcones is low due to the low solubility of the compounds. The compounds do not typically dissolve in the intestine and are therefore not available for absorption.

The spread of antimicrobial resistance determinants particular among nosocomial bacterial pathogens is an increasing problem. Such resistant pathogens include *Staphylococcus aureus* resistant to methicillin and thus to all β-lactam-antibiotics and Enterococci resistant to vancomycin (VRE). Such resistant bacteria pose a significant therapeutic challenge and bacterial strains resistant to all currently available antimicrobials are emerging. Furthermore, bacterial species intrinsically resistant to commonly employed antimicrobials are being recognized as important opportunistic pathogens in the setting of long-term immunocompromized patients. An example of this is *Stenotrophomonas maltophilia* which possesses a β-lactamase rendering the bacteria intrinsically resistant to carbapenems. As cross-resistance within a given class of antibiotics often occurs the development of new classes of antibiotics is a neccisity to counter the emerging threat of bacterial resistance.

Thus, there is a need for improved chalcone derivatives for therapeutic or prophylactic use against parasites and bacteria.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the general synthetic scheme for the preparation of aminoalkoxy-functional chalcones where the aromatic rings are phenyl rings. R^1, R^2 and Z are as defined herein.

Figure 2 illustrates a time-kill curve of III-044 against S.aureus ATCC33591. Bacterial growth is inhibited at concentrations at or above the MIC (MIC=9.4 µM). As CFU counts per ml decreases at concentrations of compound above the MIC, the compound is bactericidal. The reduction in CFU/ml is faster as the concentration of test compound increases above the MIC. This indicates that the bactericidal action of the compound is primarily dependent on the concentration of the test compound.

Figure 3 illustrates a time-kill curve of III-051 against S.aureus ATCC29213. Bacterial growth is inhibited at concentrations at or above the MIC (MIC=18.8 µM). As CFU counts per ml decreases at concentrations of compound above the MIC, the compound is bactericidal. The reduction in CFU/ml is faster as the concentration of test compound increases above the MIC. This indicates that the bactericidal action of the compound is primarily dependent on the concentration of the test compound.

Figure 4 illustrates a dose-respons curve of LicA and one of the novel aminoalkoxy-chalcones (III-056) at *Plasmodium falciparum*. As shown at the figure, III-056 is 45 times more potent than LicA.

DESCRIPTION OF THE INVENTION

The present inventors have found that the aminoalkoxy-functional chalcone defined herein exhibit interesting biological properties combined with improved metabolic and physicochemical properties which make the compound useful as drug substances, in particular as antiparasitic agents, bacteriostatic agents, and bacteriocidal agents.

It is believed that the aminoalkoxy group or groups of the aminoalkoxy-functional chalcone will be charged according to pH of the medium and the pKa of the compound. The solubility of the charged compounds is many times higher than the solubility of the neutral compounds. As the aminoalkoxy-functional chalcones will be partially charged (i.e. soluble) at the pH in the intestine, they will dissolve in the gastric juices and be available for absorption. The bioavailability of the aminoalkoxy-functional chalcones will therefore be improved many times compared to the known neutral chalcones making the compounds generally useful as drug candidates. Also, the aminoalkoxy-functional chalcones have different pKa values which enable the selection of a chalcone derivative with optimal *charged/non-charged* ratio at a given pH value.

The usefulness of the known chalcones as drug candidates have been limited by the metabolism of the compounds resulting in short half-lives *in vivo*. The inventors have now found that introduction of a aminoalkoxy group in the chalcone derivative changes the metabolic properties and the compounds prepared show improved metabolic stability.

Furthermore, the inventors have found that the aminoalkoxy-functional chalcones defined herein exhibit excellent bacteriocidal and bacteriostatic properties, even against multi-resistant bacteria strains.

Thus, the present invention provides chalcone derivatives and analogues as defined in claim 1, i.e. a compound of the general formula:

$$Y^1(X^1)\text{-}Ar^1\text{-}C(=O)\text{-}V\text{-}Ar^2(X^2)Y^2$$

wherein Ar^1 and Ar^2 independently are selected from aromatic rings (aryl) and heteroaromatic rings (heteroaryl);

V designates $-CH_2-CH_2-$, $-CH=CH-$ or $-C\equiv C-$, preferably $-CH=CH-$,

at least Y^2 of Y^1 and Y^2 represent at least one, such as 1-2, e.g. one, aminoalkoxy-functional substituent(s) of the formula

$$-O-Z-N(R^1)R^2$$

wherein Z is a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, preferably 2-4, such as 2-3, and each R^H is independently selected from hydrogen and C_{1-6}-alkyl;

R^1 and R^2 independently are selected from hydrogen, optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{4-12}-alkadienyl, optionally substituted C_{6-12}-alkatrienyl, optionally substituted C_{2-12}-alkynyl, optionally substituted C_{1-12}-alkoxycarbonyl, optionally substituted C_{1-12}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl; or R^1 and R^2 together with the nitrogen atom to which they are attached ($-N(R^1)R^2$) form an optionally substituted nitrogen-containing heterocyclic ring;

X^1 designates 0-5, preferably 0-4, such as 0-3, e.g. 0-2, substituents, and X^2 designates 1-5, preferably 1-4, such as 1-3, e.g. 1-2 substituents, where such substituents independently are selected from optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{4-12}-alkadienyl, optionally substituted C_{6-12}-alkatrienyl, optionally substituted C_{2-12}-alkynyl, hydroxy, optionally substituted C_{1-12}-alkoxy, optionally substituted C_{2-12}-alkenyloxy, carboxy, optionally substituted C_{1-12}-alkoxycarbonyl, optionally substituted C_{1-12}-alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and

di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkyl-carbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, amino-C_{1-6}-alkyl-amino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-amino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyloxy, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio, and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine;

and salts thereof.

The substituents R^1 and R^2 carried by the nitrogen atom of the aminoalkoxy substituent, are believed to slightly alter the pKa value of the chalcone derivative. Thus, the particular selection of the groups R^1 and R^2 can be used to "fine-tune" the pKa value in view of the particular condition or disease and the intended route of administration.

In one embodiment, R^1 and R^2 are independently selected from hydrogen, optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{2-12}-alkynyl, optionally substituted C_{1-12}-alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, and mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl. In particular R^1 and R^2 are independently selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{1-6}-alkylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl.

In another embodiment, R^1 and R^2 together with the nitrogen atom to which they are attached (-N(R^1)R^2) form an optionally substituted nitrogen-containing heterocyclic ring.

The selection of the substituents X^1 and X^2 is not extremely critical, although it should be noted that X^2 should represent at least one substituent. This being said, certain subgroups of substituents located in particular positions have so far proved to provide improved biological effects (see further below).

This being said, in still a further embodiment, X^1 designates 0-4, such as 0-3, e.g. 0-2, substituents, and X^2 designates 1-4, such as 1-3, e.g. 1-2, substituents, where such optional substituents independently are selected from optionally substituted C_{1-12}-alkyl, hydroxy, optionally substituted C_{1-12}-alkoxy, optionally substituted C_{2-12}-alkenyloxy, carboxy, optionally substituted C_{1-12}-alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted heteroarylcarbonyl, optionally substituted

heteroaryloxy, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkyl-carbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, amino-C_{1-6}-alkyl-amino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-amino, guanidino, carbamido, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyloxy, optionally substituted C_{1-6}-alkylthio, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, and/or halogen, in particular X^1 designates 0-3, e.g. 0-2, substituents, and X^2 designates 1-3, e.g. 1-2, substituents, where such optional substituents independently are selected from optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, carboxy, optionally substituted C_{1-6}-alkylcarbonyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, heteroarylsulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkyl-carbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, amino-C_{1-6}-alkyl-amino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-amino, guanidino, carbamido, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, and/or halogen.

The group V is relevant with respect to the spatial orientation of the rings Ar^1 and Ar^2. Thus, the group V may be $-CH_2-CH_2-$, $-CH=CH-$ or $-C\equiv C-$. Preliminary results have shown that the embodiments wherein V designates $-CH=CH-$ yields valuable chalcone derivatives.

The expression "chalcone derivative" has been assigned to the compounds of the above formula in that the overall structure namely $Ar^1-C(=O)-C-C-Ar^2$ resembles that of the chalcone structure. This being said, Ar^1 and Ar^2 are selected from aromatic rings and heteroaromatic rings. It is currently believed that particularly interesting compounds are those where at least one of Ar^1 and Ar^2, preferably both, are aromatic rings, in particular phenyl rings. This being said, the inventors envisage that the functionality of the compounds may be substantially preserved (or even improved) when one or both of Ar^1 and Ar^2 are heteroaromatic rings.

In one embodiment, at least one or Ar^1 and Ar^2 is selected from thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiophenyl, quinolyl, isoquinolyl, and indolyl.

In another embodiment, both of Ar^1 and Ar^2 are phenyl rings and Y^2 represents at least one aminoalkoxy-functional substituent, one of which being located in the 2-position of the phenyl ring, and X^2 represents at least one substituent, one of which being located in the 5-position of the phenyl ring.

In a further embodiment, X^2 represents at least one substituent selected from C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonylamino, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen, in particular from C_{1-6}-alkyl, optionally substituted phenyl, and hydroxy, e.g. from C_{1-6}-alkyl and optionally substituted phenyl. Such compounds have shown excellent bacteriostatic and bacteriocidal effects as well as antiparasitic effects (see the Examples).

In a further embodiment, which may combined with other embodiments herein, both of Ar^1 and Ar^2 are phenyl rings, and X^1 represents at least one substituent, one of which being located in the 2- or 3-position of the phenyl ring, and preferably being selected from amino-C_{1-6}-alkyl and mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl. Such compounds have shown excellent as antiparasitic effects (see the Examples).

In a still further embodiment, which may combined with other embodiments herein, both of Ar^1 and Ar^2 are phenyl rings, and X^1 represents at least one substituent, one of which being located in the 4-position of the phenyl ring, and preferably being selected from hydroxy, amino-C_{1-6}-alkylamino and mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkylamino. Such compounds have also shown excellent as antiparasitic effects (see the Examples).

This group Z is typically a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, preferably 2-4, such as 2-3, where each R^H is independently selected from hydrogen and C_{1-6}-alkyl. A particular example of Z is $-(CH_2)_n-$ wherein n is 2-4, such as 2-3.

Thus, in a particular embodiment, one of Y^1 and Y^2 represent a substituent of the formula

$$-O-(CH_2)_{2-3}-N(R^1)R^2$$

wherein R^1 and R^2 is selected from hydrogen and C_{1-6}-alkyl. Furthermore, V is preferably -CH=CH-, and Ar^1 and Ar^2 both are phenyl rings.

Definitions

In the present context, the term "bacteriostatic" is intended to describe an antimicrobial activity of a test compund, characterized by an inhibition of bacterial growth in the absence of a reduction of viable bacteria (bacterial kill) during incubation with the test compound, as evidenced in the killing curve determination by a stationary number of colony forming units (CFU) during incubation time.

In the present context, the term "bacteriocidal" is intended to describe an antimicrobial activity of a test compound, characterized by the reduction of viable bacteria (bacterial kill)

during incubation with the test compound, as evidenced in the killing curve determination by a reduction of colony forming units (CFU) during incubation time.

In the present contest, the term "antiparasitic" is intended to describe the ability of a test compound to upon incubation in vitro with a culture of parasites, e.g. *Leishmania major* or *Plasmodium falciparum*, to inhibit metabolic labelling of the parasites by at least 50% compared to mock treated control cultures.

In the present context, the term "C_{1-12}-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 12 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, butyl, *tert*-butyl, *iso*-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, cyclohexyl, etc. Analogously, the term "C_{1-6}-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, *iso*-propyl, pentyl, cyclopentyl, hexyl, cyclohexyl, and the term "C_{1-4}-alkyl" is intended to cover linear, cyclic or branched hydrocarbon groups having 1 to 4 carbon atoms, e.g. methyl, ethyl, propyl, *iso*-propyl, cyclopropyl, butyl, *iso*-butyl, *tert*-butyl, cyclobutyl.

Whenever the term "C_{1-12}-alkyl" is used herein, it should be understood that a particularly interesting embodiment thereof is "C_{1-6}-alkyl".

Similarly, the terms "C_{2-12}-alkenyl", "C_{4-12}-alkadienyl", and "C_{6-12}-alkatrienyl" are intended to cover linear, cyclic or branched hydrocarbon groups having 2 to 12, 4 to 12, and 6 to 12, carbon atoms, respectively, and comprising one, two, and three unsaturated bonds, respectively. Examples of alkenyl groups are vinyl, allyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, heptadecaenyl. Examples of alkadienyl groups are butadienyl, pentadienyl, hexadienyl, heptadienyl, heptadecadienyl. Examples of alkatrienyl groups are hexatrienyl, heptatrienyl, octatrienyl, and heptadecatrienyl. Preferred examples of alkenyl are vinyl, allyl, butenyl, especially allyl.

Similarly, the term "C_{2-12}-alkynyl" is intended to mean a linear or branched hydrocarbon group having 2 to 12 carbon atoms and comprising a triple bond. Examples hereof are ethynyl, propynyl, butynyl, octynyl, and dodecaynyl.

Whenever the terms "C_{2-12}-alkenyl", "C_{4-12}-alkadienyl", "C_{6-12}-alkatrienyl", and "C_{2-12}-alkynyl" are used herein, it should be understood that a particularly interesting embodiment thereof are the variants having up to six carbon atoms.

In the present context, i.e. in connection with the terms "alkyl", "alkenyl", "alkadienyl", "alkatrienyl", and "alkynyl", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-3 times, with group(s) selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C_{1-6}-alkoxy (i.e. C_{1-6}-alkyl-oxy), C_{2-6}-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, aryloxy, arylamino, arylcarbonyl, heteroaryl,

heteroarylamino, heteroaryloxycarbonyl, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkyl-carbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6}-alkanoyloxy, C_{1-6}-alkyl-sulphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, nitro, C_{1-6}-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl", and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine.

Preferably, the substituents are selected from hydroxy (which when bound to an unsaturated carbon atom may be present in the tautomeric keto form), C_{1-6}-alkoxy (i.e. C_{1-6}-alkyl-oxy), C_{2-6}-alkenyloxy, carboxy, oxo (forming a keto or aldehyde functionality), C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, arylcarbonyl, heteroaryl, heteroarylamino, heteroaryloxy, heteroarylcarbonyl, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbony-lamino, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, C_{1-6}-alkyl-sulphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylthio, halogen, where any aryl and heteroaryl may be substituted as specifically describe below for "optionally substituted aryl and heteroaryl".

Especially preferred examples are hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, and guanidine.

"Halogen" includes fluoro, chloro, bromo, and iodo.

In the present context the term "aryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system, such as phenyl, naphthyl, 1,2,3,4-tetrahydronaphthyl, anthracyl, phenanthracyl, pyrenyl, benzopyrenyl, fluorenyl and xanthenyl, among which phenyl is a preferred example.

The term "heteroaryl" is intended to mean a fully or partially aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms. Examples of such heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, coumaryl, furyl, thiophenyl, quinolyl, benzothiazolyl, benzotriazolyl, benzodiazolyl, benzooxozolyl, phthalazinyl, phthalanyl, triazolyl, tetrazolyl, isoquinolyl, acridinyl, carbazolyl, dibenzazepinyl, indolyl, benzopyrazolyl, phenoxazonyl. Particularly interesting heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, furyl, thiophenyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl, indolyl in

particular pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, thiophenyl, quinolyl, tetrazolyl, and isoquinolyl.

The term "heterocyclyl" is intended to mean a non-aromatic carbocyclic ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or -NH-), sulphur, and/or oxygen atoms. Examples of such heterocyclyl groups are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidine, pyroline, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, thiazetane, tetrahydrofuran, tetrahydropyran, oxepane, tetrahydrothiophene, tetrahydrothiopyrane, thiepane, dithiane, dithiepane, dioxane, dioxepane, oxathiane, oxathiepane. The most interesting examples are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane.

In the present context, i.e. in connection with the terms "aryl", "heteroaryl", and heterocyclyl, the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times) with group(s) selected from hydroxy (which when present in an enol system may be represented in the tautomeric keto form), C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, oxo (which may be represented in the tautomeric enol form), carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxy, arylamino, aryloxycarbonyl, arylcarbonyl, heteroaryl, heteroarylamino, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)-amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6}-alkyl-suphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, nitro, sulphanyl, amino, amino-sulfonyl, mono- and di(C_{1-6}-alkyl)amino-sulfonyl, dihalogen-C_{1-4}-alkyl, trihalogen-C_{1-4}-alkyl, halogen, where aryl and heteroaryl representing substituents may be substituted 1-3 times with C_{1-4}-alkyl, C_{1-4}-alkoxy, nitro, cyano, amino or halogen, and any alkyl, alkoxy, and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine.

Preferably, the substituents are selected from hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, oxo (which may be represented in the tautomeric enol form), carboxy, C_{1-6}-alkylcarbonyl, formyl, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, C_{1-6}-alkyl-sulphonyl-amino, aryl-sulphonyl-amino, heteroaryl-sulphonyl-amino, C_{1-6}-alkyl-suphonyl, C_{1-6}-alkyl-sulphinyl, C_{1-6}-alkylsulphonyloxy, sulphanyl, amino, amino-sulfonyl, mono- and

di(C_{1-6}-alkyl)amino-sulfonyl or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine. Especially preferred examples are C_{1-6}-alkyl, C_{1-6}-alkoxy, amino, mono- and di(C_{1-6}-alkyl)amino, sulphanyl, carboxy or halogen, where any alkyl, alkoxy and the like representing substituents may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine.

In the present context the term "nitrogen-containing heterocyclic ring" is intended to mean heterocyclic ring or ring system in which at least one nitrogen atom is present. Such a nitrogen is, with reference to the formula, carrying the substituents R_1 and R_2. The heterocyclic ring or ring system is a ring or ring system where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen (=N- or –N-), sulphur, and/or oxygen atoms. Examples of such rings are aromatic rings such as pyridine, pyridazine, pyrimidine, pyrazine, triazine, thiophene, oxazole, isoxazole, thiazole, isothiazole, pyrrole, imidazole, pyrazole, tetrazole, quinoline, benzothiazole, benzotriazole, benzodiazole, benzoxozole, triazole, isoquinoline, indole, benzopyrazole, thiadiazole, and oxadiazole. The most interesting examples of aromatic rings are pyridine, pyridazine, pyrimidine, pyrazine, thiophene, tetrazole, oxazole, isoxazole, thiazole, isothiazole, pyrrole, imidazole, pyrazole, quinoline, triazole, isoquinoline, and indole, in particular pyridine, thiophene, imidazole, quinoline, isoquinoline, indole, and tetrazole.

Other examples of such rings are non-aromatic rings such as imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, aziridine, azirine, azetidine, pyroline, tropane, oxazinane (morpholine), azepine, dihydroazepine, tetrahydroazepine, and hexahydroazepine, oxazolane, oxazepane, oxazocane, thiazolane, thiazinane, thiazepane, thiazocane, oxazetane, diazetane, and thiazetane. The most interesting examples of non-aromatic rings are imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, diazocane, pyrrolidine, piperidine, azepane, azocane, azetidine, tropane, oxazinane (morpholine), oxazolane, oxazepane, thiazolane, thiazinane, and thiazepane, in particular imidazolidine, piperazine, hexahydropyridazine, hexahydropyrimidine, diazepane, pyrrolidine, piperidine, azepane, oxazinane (morpholine), and thiazinane.

In the present context, i.e. in connection with the term "nitrogen-containing heterocyclic ring", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, in particular 1-3 times) with group(s) selected from the same substituents as defined above for "optionally substituted aryl".

As it will be evident from the formulae defined herein and the definitions associated therewith, there may be one or several asymmetric carbon atoms present in the compounds depending on the nature of the substituents. The compounds are intended to

include all stereoisomers arising from the presence of any and all isomers as well as mixtures thereof, including racemic mixtures.

It should furthermore be understood that the compounds defined herein include possible salts thereof, of which pharmaceutically acceptable salts are of course especially relevant for the therapeutic applications. Salts include acid addition salts and basic salts. Examples of acid addition salts are hydrochloride salts, fumarate, oxalate, etc. Examples of basic salts are salts where the (remaining) counter ion is selected from alkali metals, such as sodium and potassium, alkaline earth metals, such as calcium salts, potassium salts, and ammonium ions ($^{+}N(R')_4$, where the R''s independently designates optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-6}-alkenyl, optionally substituted aryl, or optionally substituted heteroaryl). Pharmaceutically acceptable salts are, e.g., those described in Remington's - The Science and Practice of Pharmacy, 20th Ed. Alfonso R.Gennaro (Ed.), Lippincott, Williams & Wilkins; ISBN: 0683306472, 2000, and in Encyclopedia of Pharmaceutical Technology.

Thus, chalcones with aminoalkoxy groups can be prepared in their salt-forms thereby making the compounds particularly useful for pharmaceutical formulations. The use of appropriate selected salt form can be used to control the dissolution rate in vivo. Furthermore, the different salt forms have different bulk-properties that is of importance for the manufacturing process.

Preparation of compounds

The aminoalkoxy-functional chalcones defined herein may be produced by methods known *per se* for the preparation of chalcones or methods that are analogous to such methods. Examples of excellent methods for preparing compounds of the 1,3-bis-aromatic-prop-2-enone or the 1,3-bis-aromatic-prop-2-ynone types are given in the following. Further examples of methods for the preparation of the compound used according to the present invention are described in WO 95/06628 and WO 93/17671 and in the references cited therein.

Compounds of the general formula I in which V is -CH=CH- can be prepared by reacting a ketone (an acetophenone in the case where Ar^1 is phenyl)

$$Y^1(X^1)\text{-}Ar^1\text{-}C(=O)\text{-}CH_3$$

with an aldehyde (a benzaldehyde in the case where Ar^2 is phenyl)

$$HCO\text{-}Ar^2\text{-}(X^2)Y^2$$

wherein Ar^1, Ar^2, X^1, X^2, Y^1, and Y^2 refers to the definitions given elsewhere herein.

This reaction, which is a condensation reaction, is suitably carried out under acid or base catalysed conditions. A review of such processes may be found in Nielsen, A.T., Houlihahn, W.J., *Org. React.* **16**, 1968, p 1-444. In particular the method described by Wattanasin, S. and Murphy, S., *Synthesis* (1980) 647 has been found quite successful. The reaction may suitably be carried out in protic organic solvents, such as lower alcohols (e.g. methanol, ethanol, or tert-butanol), or lower carboxylic acids (formic, glacial acetic, or propionic acid), or in aprotic organic solvents such as ethers (e.g. tetrahydrofuran, dioxane, or diethyl ether), liquid amides (e.g. dimethylformamide or hexamethylphosphordiamide), dimethylsulfoxide, or hydrocarbons (e.g. toluene or benzene), or mixtures of such solvents. When carrying out the reaction under base catalysed conditions, the catalyst may be selected from sodium, lithium, potassium, barium, calcium, magnesium, aluminum, ammonium, or quaternary ammonium hydroxides, lower alkoxides (e.g. methoxides, ethoxides, tert-butoxides), carbonates, borates, oxides, hydrides, or amides of lower secondary amines (e.g. diisopropyl amides or methylphenyl amides). Primary aromatic amines such as aniline, free secondary amines such as dimethyl amine, diethyl amine, piperidine, or pyrrolidine as well as basic ion exchange resins may also be used.

Acid catalysts may be selected from hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, sulfonic acids (such as paratoluenesulfonic or methanesulfonic acid), lower carboxylic acids (such as formic, acetic or propionic acid), lower halogenated carboxylic acids (such as trifluoroacetic acid), Lewis acids (such as BF_3, $POCl_3$, PCl_5, or $FeCl_3$), or acid ion exchange resins.

A drawback of the base catalysed condensation is the poor yield obtained if the aromatic ring in which the ketone or the aldehyde or both is substituted with one or more hydroxy groups. This drawback can be overcome by masking the phenolic group as described by T. Hidetsugu et al. in EP 0 370 461. Deprotection is easily performed by mineral acids such as hydrochloric acid.

The reaction is typically carried out at temperatures in the range of 0-100°C, e.g. at room temperature. Reaction times are typically from 30 min to 24 hours.

The starting materials for the synthesis (acetophenone and benzaldehyde), may be obtained from commercial sources or may be synthesised according to well-known methods. The aminoalkoxy-benzaldehydes and aminoalkoxy-acetophenones can be synthesized by alkylation of the corresponding hydroxy-benzaldehydes or hydroxy-acetophenones (Figure 1). Alternatively the aminoalkoxy-chalcones can be prepared by alkylation of the corresponding hydroxy-chalcone.

Compounds of the general formula I in which V is -C≡C- may be prepared by reacting an activated derivative of a carboxylic acid of the general formula

$$Y^1(X^1)\text{-}Ar^1\text{-}COOH$$

with an ethyne derivative

$$H\text{-}C{\equiv}C\text{-}Ar^2\text{-}(X^2)Y^2$$

wherein Ar^1, Ar^2, X^1, X^2, Y^1, and Y^2 refers to the definitions given elsewhere herein.

Reactions of this type are described by Tohda, Y., Sonogashihara, K., Haghara, N., *Synthesis* **1977**, p 777-778. It is contemplated that the activated derivative of the carboxylic acid may be an activated ester, an anhydride or, preferably, an acid halogenide, in particular the acid chloride. The reaction is normally carried out using the catalysts described by Tohda, Y. *et al.* cited above, namely copper(I)iodide/triphenylphosphine-palladium dichloride. The reaction is suitably carried out in triethylamine, a mixture of triethylamine and pyridine or triethylamine and toluene under a dry inert atmosphere such as nitrogen or argon. The reaction is generally carried out at reduced temperature such as in the range from -80°C to room temperature, the reaction time typically being from 30 minutes to 6 hours.

In the above reactions, it may be preferred or necessary to protect various sensitive or reactive groups present in the starting materials to prevent said groups from interfering with the reactions. Such protection may be carried out in a well-known manner, e.g. as described in "Protective Groups in Organic Chemistry" by Wuts and Greene, Wiley-Interscience; ISBN: 0471160199; 3nd edition (May 15, 1999). For example, in the reaction between the activated acid derivative and the acetylene derivative, a hydroxy group on Ar^1 and/or Ar^2 may be protected in the form of the methoxymethyl ether, N,N-dimethylcarbamoyl ester, or allyl ether. The protecting group may be removed after the reaction in a manner known *per se*.

The ethyne derivative may be prepared by standard methods, e.g. as described by Nielsen, S. F. Et al., Bioorg. Med. Chem. 6, pp 937-945 (1998). The carboxylic acids may likewise be prepared by standard procedures, e.g. as described in the examples.

Compounds of the general formula I in which V is $-CH_2-CH_2-$ can be prepared by ionic hydrogenation of the corresponding α,β-unsaturated compound where V is –CH=CH- as it has been described by the inventors in Nielsen, S.F. et al. Tetrahedron, 53, pp 5573-5580 (1997).

Further possible synthetic routes for the preparation of the saturated variants are described in "Advanced Organic Chemistry" by Jerry March, 3rd ed. (especially chapter 15, pages 691-700) and references cited therein. Thus, it is possible to obtain a large variety of compounds of the 1,3-bis-aromatic-propan-1-one type from the corresponding prop-2-en-1-ones.

Medical uses

It has been demonstrated herein (see the Examples section) that the novel compound have interesting properties as bacteriostatic, bacteriocidal and antiparasitic agents. It is of course possible that the compounds also have other interesting properties to be utilised in the medical field.

Thus, the present invention provides a compound (chalcone derivative) as defined herein for use as a drug substance.

In particular, the chalcone derivative may be used for the treatment of bacterial infections in a mammal in need thereof. Such bacterial infection may be caused by common Gram-positive and Gram-negative pathogens as well as microaerophilic and anaerobic bacteria. As a particularly relevant example of a bacteria against which chalcone derivatives have effect can be mentioned antibiotic-sensitive and -resistant strains of *S.aureus* and *E.faecium*. Other examples common causes of community acquired and nosocomial respiratory infections including *S.pneumoniae*, *S.pyogenes* and members of *Enterobacteriaceae* (e.g. *E.coli*), microaerophilic bacteria associated with gastric disease (e.g. *Helicobacter pylori*) and pathogenic anaerobic bacteria (e.g. *Bacteroides fragilis* and *Clostridium species*).

Also, the chalcone derivatives can be used for the treatment of infections caused by protozoa in a mammal. Examples of infections are those caused by a protozoa selected from *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae*.

Furthermore, the chalcone derivatives can be used for the preparation of a pharmaceutical composition for the treatment of infections in a mammal caused by *Leishmania spp.* Such infections may be cutaneous and/or visceral.

Preliminary results have shown that compounds wherein the Y^2 is the aminoalkoxy-substituent positioned in the 2 position where Ar^1 is phenyl, are particularly promising for the treatment of infections caused by Plasmodium. Those in which X^2 represents at least one substituent selected from C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonylamino, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen, in particular from C_{1-6}-alkyl, optionally substituted phenyl, and hydroxy, e.g. from C_{1-6}-alkyl and optionally substituted phenyl, appear to be particularly promising. Particular examples of efficient chalcone derivatives are those where X^1 represents at least one substituent, one of which being located in the 2- or 3-position of the phenyl ring, and preferably being selected from amino-C_{1-6}-alkyl and mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl, or those where X^1 represents at least one substituent, one of which being located in the 4-position of the phenyl ring, and preferably being

selected from hydroxy, amino-C_{1-6}-alkylamino and mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkylamino.

Other preliminary results have shown that compounds wherein the Y^2 is the aminoalkoxy-substituent positioned in the 2 position where Ar^1 is phenyl, are particularly promising for the treatment of infections caused by *Leishmania spp*. Those in which X^2 represents at least one substituent selected from C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonylamino, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen, in particular from C_{1-6}-alkyl, optionally substituted phenyl, and hydroxy, e.g. from C_{1-6}-alkyl and optionally substituted phenyl, appear to be particularly promising.

Still other preliminary results indicate that compounds wherein the Y^2 is the aminoalkoxy-substituent positioned in the 2 position where Ar^1 is phenyl, are particularly promising for the treatment of infections caused by *S. aureus*. Those in which X^2 represents at least one substituent selected from C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonylamino, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen, in particular from C_{1-6}-alkyl, optionally substituted phenyl, and hydroxy, e.g. from C_{1-6}-alkyl and optionally substituted phenyl, appear to be particularly promising.

The chalcone derivatives are typically formulated in a pharmaceutical composition prior to use as a drug substance.

Formulation of pharmaceutical compositions

The administration route of the compounds (aminoalkoxy-functional chalcones) as defined herein may be any suitable route that leads to a concentration in the blood or tissue corresponding to a therapeutic concentration. Thus, e.g., the following administration routes may be applicable although the invention is not limited thereto: the oral route, the parenteral route, the cutaneous route, the nasal route, the rectal route, the vaginal route and the ocular route. It should be clear to a person skilled in the art that the administration route is dependant on the particular compound in question, particularly, the choice of administration route depends on the physico-chemical properties of the compound together with the age and weight of the patient and on the particular disease or condition and the severity of the same.

The compounds as defined herein may be contained in any appropriate amount in a pharmaceutical composition, and are generally contained in an amount of about 1-95% by

weight of the total weight of the composition. The composition may be presented in a dosage form which is suitable for the oral, parenteral, rectal, cutaneous, nasal, vaginal and/or ocular administration route. Thus, the composition may be in form of, e.g., tablets, capsules, pills, powders, granulates, suspensions, emulsions, solutions, gels including hydrogels, pastes, ointments, creams, plasters, drenches, delivery devices, suppositories, enemas, injectables, implants, sprays, aerosols and in other suitable form.

The pharmaceutical compositions may be formulated according to conventional pharmaceutical practice, see, e.g., "Remington's Pharmaceutical Sciences" and "Encyclopedia of Pharmaceutical Technology", edited by Swarbrick, J. & J. C. Boylan, Marcel Dekker, Inc., New York, 1988. Typically, the compounds defined herein are formulated with (at least) a pharmaceutically acceptable carrier or exipient. Pharmaceutically acceptable carriers or exipients are those known by the person skilled in the art.

Thus, the present invention provides a pharmaceutical composition comprising a compound as defined herein in combination with a pharmaceutically acceptable carrier.

Pharmaceutical compositions according to the present invention may be formulated to release the active compound substantially immediately upon administration or at any substantially predetermined time or time period after administration. The latter type of compositions are generally known as controlled release formulations.

In the present context, the term "controlled release formulation" embraces i) formulations which create a substantially constant concentration of the drug within the body over an extended period of time, ii) formulations which after a predetermined lag time create a substantially constant concentration of the drug within the body over an extended period of time, iii) formulations which sustain drug action during a predetermined time period by maintaining a relatively, constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with fluctuations in the plasma level of the active drug substance (sawtooth kinetic pattern), iv) formulations which attempt to localize drug action by, e.g., spatial placement of a controlled release composition adjacent to or in the diseased tissue or organ, v) formulations which attempt to target drug action by using carriers or chemical derivatives to deliver the drug to a particular target cell type.

Controlled release formulations may also be denoted "sustained release", "prolonged release", "programmed release", "time release", "rate-controlled" and/or "targeted release" formulations.

Controlled release pharmaceutical compositions may be presented in any suitable dosage forms, especially in dosage forms intended for oral, parenteral, cutaneous nasal, rectal, vaginal and/or ocular administration. Examples include single or multiple unit tablet or capsule compositions, oil solutions, suspensions, emulsions, microcapsules, microspheres,

nanoparticles, liposomes, delivery devices such as those intended for oral, parenteral, cutaneous, nasal, vaginal or ocular use.

Preparation of solid dosage forms for oral use, controlled release oral dosage forms, fluid liquid compositions, parenteral compositions, controlled release parenteral compositions, rectal compositions, nasal compositions, percutaneous and topical compositions, controlled release percutaneous and topical compositions, and compositions for administration to the eye can be performed essentially as described in the applicant's earlier International application No. WO 99/00114, page 29, line 9, to page 40, line 3. Also, and more generally, the formulation and preparation of the above-mentioned compositions are well-known to those skilled in the art of pharmaceutical formulation. Specific formulations can be found in "Remington's Pharmaceutical Sciences".

Dosages

The compound are preferably administered in an amount of about 0.1-50 mg per kg body weight per day, such as about 0.5-25 mg per kg body weight per day.

For compositions adapted for oral administration for systemic use, the dosage is normally 2 mg to 1 g per dose administered 1-4 times daily for 1 week to 12 months depending on the disease to be treated.

The dosage for oral administration for the treatment of parasitic diseases is normally 1 mg to 1 g per dose administered 1-2 times daily for 1-4 weeks, in particular the treatment of malaria is to be continued for 1-2 weeks whereas the treatment of leishmaniasis will normally be carried out for 3-4 weeks.

The dosage for oral administration for the treatment of bacterial diseases is normally 1 mg to 1 g per dose administered 1-4 times daily for 1 week to 12 months; in particular, the treatment of tuberculosis will normally be carried out for 6-12 months.

The dosage for oral administration of the composition in order to prevent diseases is normally 1 mg to 75 mg per kg body weight per day. The dosage may be administered once or twice daily for a period starting 1 week before the exposure to the disease until 4 weeks after the exposure.

For compositions adapted for rectal use for preventing diseases, a somewhat higher amount of the compound is usually preferred, i.e. from approximately 1 mg to 100 mg per kg body weight per day.

For parenteral administration, a dose of about 0.1 mg to about 50 mg per kg body weight per day is convenient. For intravenous administration a dose of about 0.1 mg to about 20 mg per kg body weight per day administered for 1 day to 3 months is convenient. For intraarticular administration a dose of about 0.1 mg to about 20 mg per kg body weight

per day is usually preferable. For parenteral administration in general, a solution in an aqueous medium of 0.5-2% or more of the active ingredients may be employed.

For topical administration on the skin, a dose of about 1 mg to about 5 g administered 1-10 times daily for 1 week to 12 months is usually preferable.

In many cases, it will be preferred to administer the compound defined herein together with another antiparasitic, antimycotic or antibiotic drug, thereby reducing the risk of development of resistance against the conventional drugs, and reducing the amount of each of the drugs to be administered, thus reducing the risk of side effects caused by the conventional drugs. Important aspects of this is the use of the compound against Leishmania, where the compound is combined with another antileishmanial drug, or the antimalarial use of the compound where the compound is used together with another antimalarial drug.

Method of prediction

In a separate aspect, the present invention also provides a method of predicting whether a chemical compound has a potential inhibitory effect against a microorganism selected from *Helicobacter pylori* and *Plasmodium falciparum*, said method comprising preparing a mixture of a dihydroorotate dehydrogenase, a substrate for dihydroorotate dehydrogenase and the chemcial compound, measuring the enzymatic activity of dihydroorotate dehydrogenase (A), comparing the enzymatic activity of dihydroorotate dehydrogenase (A) with the standard activity of dihydroorotate dehydrogenase (B) corresponding to the activity of a dihydroorotate dehydrogenase in a similar sample, but without the chemical compound, predicting that the chemical compound has a potential inhibitory effect against *Helicobacter pylori* and *Plasmodium falciparum* if A is significantly lower than B.

The method can be performed as described under *DHODH Assay* in the Examples section. It should be noted that the method is not only applicable for the chalcone derivatives defined herein, but can be generally applied to predict the potential inhibitory effect of any compound. Preferably, however, the chemical compound is a chalcone derivative, e.g. a chalcone derivative as defined herein.

EXAMPLES

Preparation of compounds

The general method for the preparation of the A ring or B ring having the aminoalkoxy-functional group is illustrated in Figure 1.

General procedure A

Preparation of alkyl- or dialkyl aminomethyl acetophenones

To a solution of (2-methyl-[1,3]dioxan-2-yl) benzaldehyde (165 mmol) and amine (247 mmol) in dry THF (1.5 L) was added sodium triacetoxyborohydride (257mmol) under argon. The resulting suspension was stirred at room temperature for 18 hr. A solution of sodium hydroxide (2M) was added and stirring was continued for approximately 30 min, before the mixture was acidified using HCl (6M). The mixture was stirred for 1 hr. and extracted with diethyl ether, which was discarded. The pH of the aqueous phase was adjusted to 11 – 14 using sodium hydroxide and extracted again with diethyl ether. The latter organic phase, was dried (Na_2SO_4), filtered and evaporated to give the title products, which were used without further purification.

General procedure B

Preparation of amino acetophenones

3'- or 4'-bromoacetophenone ketal (40 mmol), amine (48 mmol), $Pd_2(dba)_3$ (0.2 mmol, 1 mol% Pd), *rac*-BINAP (0.6 mmol) and Na-*t*-OBu (68 mmol) was stirred in degassed toluene (60 mL) at 80°C for 18 h. The darkbrown mixture was poured into icecold hydrochloric acid (1 M, 200 mL) and stirred vigorously for 2 hours at 25°C. The solution was cooled to 0°C and pH was adjusted to 13 using 6M NaOH(aq) and extracted with Et_2O (4 x 100 mL). The organic phase was dried (K_2CO_3) and the solvent was removed under reduced pressure. The resulting crude oil purified by flash chromatography using 5% Et_3N in EtOAc.

General procedure C

Preparation of (2-dimethylaminoethoxy)- acetophenones

A solution of hydroxy acetophenone (48 mmol), 2-(dimethylamino)ethyl chloride, HCl (96 mmol) and K2CO3 (48 mmol) in dry DMF (300 mL) was refluxed overnight. The reaction was cooled to room temperature and added 2 M NH_3 solution (aq) (600 mL) and extracted with diethyl ether. The combined organic phases were dried (Na_2SO_4) and evaporated *in vacuo*. The residue purified by column chromatography gave the title compound.

General procedure D

Preparation of (3-dimethylaminopropoxy)- acetophenones

A solution of hydroxy acetophenone (48 mmol), 3-(dimethylamino)propyl chloride, HCl (96 mmol) and 60% NaH (48 mmol) in dry DMF (300 mL) was heated to 100°C for 3h. The reaction was cooled to room temperature and added 2 M NH_3 solution (aq) (600 mL) and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic phases were dried (Na_2SO_4)

and evaporated *in vacuo*. The resulting yellow solution was redissolved in water (500 mL) and extracted with diethyl ether. The combined organic phases were dried (Na_2SO_4) and evaporated *in vacuo*. The residue purified by column chromatography gave the title compound.

General procedure E

Preparation of (2-dimethylaminoethoxy)-benzaldehydes

A stirred solution of hydroxybenzaldehyde (59.7 mmol) in dry toluene (200 mL) and DMSO (1 mL) was added 60% NaH (60 mmol) under ice cooling. The reaction was slowly heated to room temperature. 2-(dimethylamino)ethyl chloride, HCl (110 mmol) dissolved in water (50 mL) was added NaOH (110 mmol) and the aqueous phase was extracted with toluene (3 x 30 mL). The combined organic phases were dried (Na_2SO_4) and slowly added to the reaction. The solution was heated to 90°C for 16 h. The reaction mixture was cooled to room temperature and washed with water (3 x 100 mL), 2N NaOH (100 mL) and dried (Na_2SO_4). Evaporation *in vacuo* gave the title products.

General procedure F

Preparation of (3-dimethylaminopropoxy)-benzaldehydes

A stirred solution of hydroxybenzaldehyde (59.7 mmol) in dry toluene (200 mL) and DMSO (1 mL) was added 60% NaH (60 mmol) under ice cooling. The reaction was slowly heated to room temperature. 3-Dimethylaminopropylchloride, HCl (110 mmol) dissolved in water (50 mL) was added NaOH (110 mmol) and the aqueous phase was extracted with toluene (3 x 30 mL). The combined organic phases were dried (Na_2SO_4) and slowly added to the reaction. The solution was heated to 90°C for 16 h. The reaction mixture was cooled to room temperature and washed with water (3 x 100 mL), 2N NaOH (100 mL) and dried (Na_2SO_4). Evaporation *in vacuo* gave the title products.

General procedure G

Preparation of biaryl carbaldehydes

A solution of Na_2CO_3 (44 mmol) in water (20 mL) was added to a solution of bromobenzaldehyde (14.7 mmol) and (hetero)arylboronic acid (17.6 mmol) in DME (40 mL). The mixture was flushed with argon for 2 minutes followed by addition of $Pd(PPh_3)_2Cl_2$ (310 mg, 3 mol %). The reaction was heated at reflux and left overnight under an atmosphere of argon. The reaction was cooled, 2M Na_2CO_3 was added, and the mixture

was extracted with EtOAc (3 x 20 mL). The title products were purified by flash chromatography.

General procedure H

Synthesis of chalcones

To a solution of an acetophenone (2 mmol) and a benzaldehyde (2 mmol) in 96% EtOH (10 mL) was added 8M NaOH (0.3 mL), and the mixture was stirred for 3-18 hours at 25°C. The mixture was evaporated on Celite® and the product was isolated by flash chromatography. The aminochalcone was dissolved in MeOH:Et_2O (1:9 v/v, 10 mL) and a solution of fumaric acid or oxalic acid in MeOH:Et_2O (1:9 v/v) was added. The salt was filtered off and recrystallised from MeOH or MeCN. Some aminochalcones did not undergo saltformation, and was isolated as the free base. The purity was >95% determined by HPLC and the molecular weight was determined by LC-MS.

General procedure I

Preparation of (2-dimethylaminoethoxy)- chalcones

A solution of hydroxy chalcone (3.5 mmol), 2-(dimethylamino)ethyl chloride, HCl (3.5 mmol) and K_2CO_3 (10.5 mmol) in dry DMF (20 mL) was heated to reflux for 3h. The reaction was cooled to room temperature and added 2 M NH_3 solution (aq) and extracted with ether. The combined organic phases were dried (Na_2SO_4) and evaporated *in vacuo*. The residue purified by column chromatography gave the title compound.

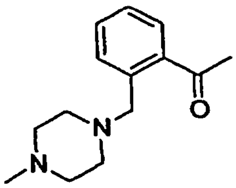
General procedure J

Synthesis of quaternary ammonia salt

Iodomethane (1 mmol) was added to a solution of the amine (1mmol) in THF (10 ml) and stirring was continued for 16 hours. The product precipitate as crystals.

Acetophenones

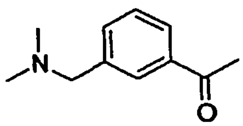
III-001: 1-[2-(4-Methyl-piperazin-1-ylmethyl)-phenyl]-ethanone



General procedure A gave the title compound as a brown oil in 78% yield.

^{1}H-NMR ($CDCl_3$) δ 7.42-7.29 (m, 4H), 3.65 (s, 2H), 2.54 (s, 3H), 2.43 (b, 8H), 2.27 (s, 3H).

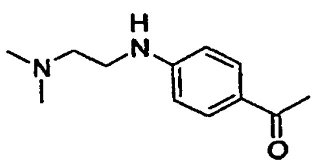
III-002: 1-(3-Dimethylaminomethyl-phenyl)-ethanone



General procedure A gave the title product as yellow oil in 89% yield.

^{1}H-NMR ($CDCl_3$) δ 7.89 (s, 1H), 7.85 (d, 1H), 7.52 (d, 1H), 7.42 (t, 1H), 3.47 (s, 2H), 2.61 (s, 3H), 2.25 (s, 6H).

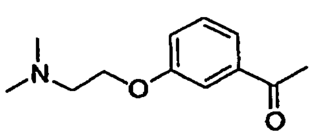
III-003: 1-[4-(2-Dimethylamino-ethylamino)-phenyl]-ethanone



General procedure B gave the title product as brown oil in 86% yield.

^{1}H NMR ($CDCl_3$) δ 7.76 (d, 2H), 6.50 (d, 2H), 4.90 (bs, 1H), 3.13 (q, 2H), 2.50 (t, 2H), 2.43 (s, 3H), 2.19 (s, 6H).

III-004: 1-[3-(2-Dimethylamino-ethoxy)-phenyl]-ethanone

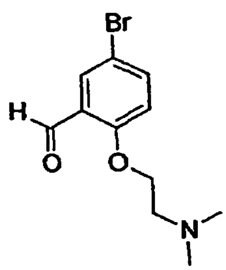


General procedure C gave the title product as brown oil in 26% yield.

^1H NMR ($CDCl_3$) δ 7.45-7.39 (m, 2H), 7.26 (t, 1H), 7.03 (ddd, 1H), 4.04 (t, 2H), 2.69 (t, 2H), 2.49 (s, 3H), 2.28 (s, 9H).

Benzaldehydes

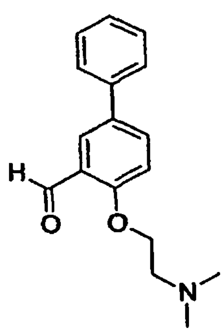
III-005: 5-Bromo-2-(2-dimethylamino-ethoxy)-benzaldehyde



General procedure E gave the title compound as a yellow oil in 65 % yield.

^1H NMR ($CDCl_3$) δ 10.43 (s, 1H), 7.94 (d, 1H), 7.63 (dd, 1H), 6.92 (d, 1H), 4.19 (t, 2H), 2.81 (t, 2H), 2.37 (s, 6H).

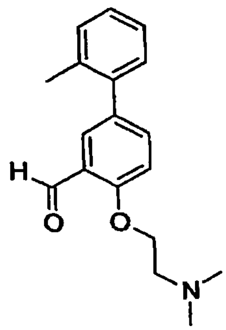
III-006: 4-(2-Dimethylamino-ethoxy)-biphenyl-3-carbaldehyde



General procedure G gave the title compound as yellow crystals in 57% yield.

^1H NMR ($CDCl_3$) δ 10.48 (s, 1H), 8.01 (d, 1H), 7.71 (dd, 1H), 7.49 (d, 1H), 7.36 (t, 2H), 7.26 (t, 1H), 7.00 (d, 1H), 4.18 (t, 2H), 2.77 (t, 2H), 2.31 (s, 6H).

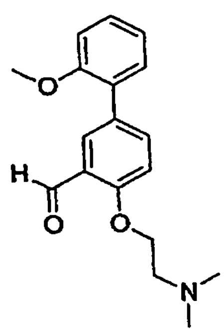
III-007: 4-(2-Dimethylamino-ethoxy)-2'-methyl-biphenyl-3-carbaldehyde



General procedure G gave the title compound as white crystals in 79% yield.

^{1}H-NMR($CDCl_3$) δ 10.56 (s, 1H), 7.82 (d, 1H), 7.51 (dd, 1H), 7.28-7.16 (m, 4H), 7.05 (d, 1H), 4.25 (t, 2H), 2.84 (t, 2H), 2.38 (s, 6H), 2.26 (s, 3H).

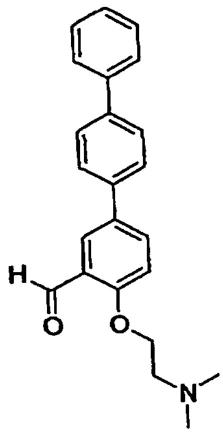
III-008: 4-(2-Dimethylamino-ethoxy)-2'-methoxy-biphenyl-3-carbaldehyde



General procedure G gave the title compound as light yellow crystals in 78% yield.

^{1}H-NMR(DMSO-d_6) δ 10.40 (s, 1H), 7.80-7.72 (m, 2H), 7.38-7.25 (m, 3H), 7.11 (d, 1H), 7.03 (t, 1H), 4.25 (t, 2H), 3.76 (s, 3H), 2.72 (t, 2H), 2.25 (s, 6H).

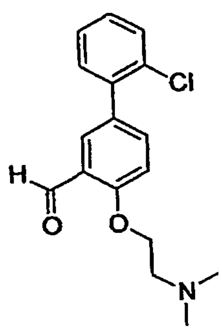
III-009: 4-(2-Dimethylamino-ethoxy)-[1,1';4',1"]terphenyl-3-carbaldehyde



General procedure G gave the title compound as light yellow crystals in 31% yield.

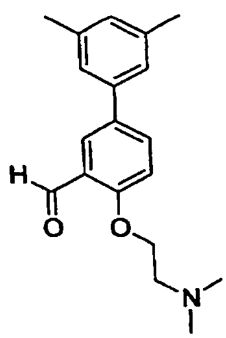
^{1}H NMR ($CDCl_3$) δ 10.49 (s, 1H), 8.06 (d, 1H), 7.76 (dd, 1H), 7.59-7.55 (m, 6H), 7.39 (dd, 2H), 7.31 (dd, 1H), 7.02 (d, 1H), 4.18 (t, 2H), 2.77 (t, 2H), 2.31 (s, 6H).

III-010: 2'-Chloro-4-(2-dimethylamino-ethoxy)-biphenyl-3-carbaldehyde



General procedure G gave the title compound.

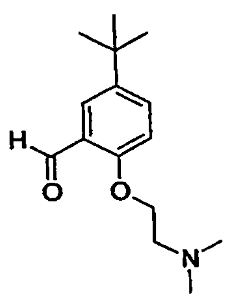
III-011: 4-(2-Dimethylamino-ethoxy)-3',5'-dimethyl-biphenyl-3-carbaldehyde



General procedure G gave the title compound as colourless crystals in 81% yield.

^{1}H NMR (DMSO-d_6) δ 10.41 (s, 1H), 7.94-7.89 (m, 2H), 7.33 (d, 1H), 7.24 (bs, 2H), 6.98 (bs, 1H), 4.25 (t, 2H), 2.71 (t, 2H), 2.32 (s, 6H), 2.24 (s, 6H).

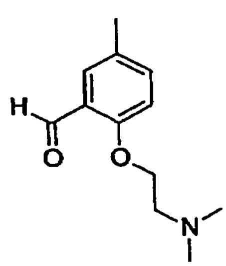
III-012: 5-*tert*-Butyl-2-(2-dimethylamino-ethoxy)-benzaldehyde



General procedure E gave the title product as yellow oil in 93% yield.

^{1}H NMR ($CDCl_3$) δ 10.50 (s, 1H), 7.85 (d, 1H), 7.57 (dd, 1H), 6.93 (d, 1H), 4.18 (t, 2H), 2.79 (t, 2H), 2.36 (s, 6H), 1.31 (s, 9H).

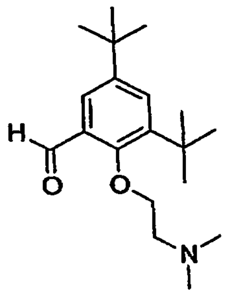
III-013: 2-(2-Dimethylamino-ethoxy)-5-methyl-benzaldehyde



General procedure E gave the title product as yellow oil in 95% yield.

^1H NMR ($CDCl_3$) δ 10.48 (s, 1H), 7.63 (d, 1H), 7.34 (dd, 1H), 6.89 (d, 1H), 4.16 (t, 2H), 2.79 (t, 2H), 2.35 (s, 6H), 2.31 (s, 3H).

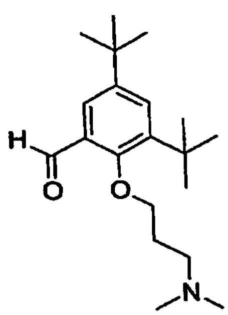
III-014: 3,5-Di-*tert*-butyl-2-(2-dimethylamino-ethoxy)-benzaldehyde



General procedure E gave the title product as yellow oil in 35% yield.

^1H NMR ($CDCl_3$) δ 10.39 (s, 1H), 7.72 (d, 1H), 7.63 (d, 1H), 4.05 (t, 2H), 2.83 (t, 2H), 1.45 (s, 6H), 1.33 (s, 9H), 1.29 (s, 9H).

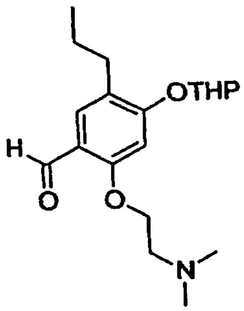
III-015: 5-*tert*-Butyl-2-(3-dimethylaminopropoxy)benzaldehyde



General procedure F gave the title product as yellow oil in 56% yield.

^1H NMR ($CDCl_3$) δ 10.52 (s, 1H), 7.86 (d, 1H), 7.58 (dd, 1H), 6.96 (d, 1H), 4.15 (t, 2H), 2.49 (t, 2H), 2.27 (s, 6H), 2.02 (hep, 2H), 1.33 (s, 9H).

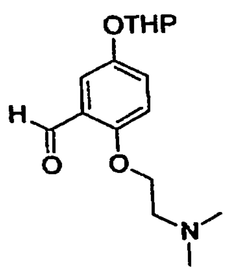
III-016: 2-(2-Dimethylamino-ethoxy)-5-propyl-4-(tetrahydro-pyran-2-yloxy)-benzaldehyde

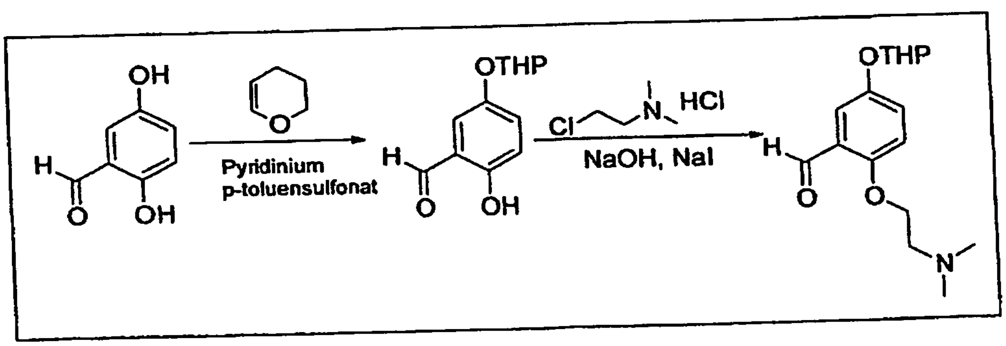


General procedure E gave the title compound as brown crystals in 15% yield.

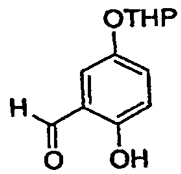
^1H NMR ($CDCl_3$) δ 10,36 (s, 1H); 7,65 (s, 1H); 6,78 (s, 1H); 5,56 (s, 1H); 4,24-4,12 (m, 2H); 3,88-3,64 (m, 2H); 2,81 (t, 2H); 2,61-2,55 (m, 2H); 2,38 (s, 6H); 2,05-1,57 (m, 8H); 0,96 (t, 3H).

III-017: 2-(2-Dimethylamino-ethoxy)-5-(tetrahydro-pyran-2-yloxy)-benzaldehyde





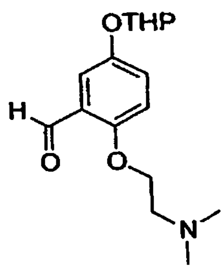
III-018: 2-Hydroxy-5-(tetrahydro-pyran-2-yloxy)-benzaldehyde



A solution of 2,5-dihydroxy-benzaldehyde (152 mmol), 3,4-dihydro-2H-pyran (167 mmol) and a catalytic amount of pyridinium p-toluenesulfonate in CH_2Cl_2 (480 mL) was left overnight at room temperature. The organic phase was washed with 1 N Na_2CO_3 (aq) (3 x 100 mL) and dried (Na_2SO_4). Evaporation *in vacuo* gave the desired product as brown crystals that was used without further purification.

^{1}H NMR ($CDCl_3$) δ 10.72 (s, 1H), 9.88 (s, 1H), 7.32-7.29 (m, 2H), 6.96 (d, 1H), 5.38 (bs, 1H), 3.99-3.91 (m, 1H), 3.69-3.64 (m, 1H), 2.06-1.63 (m, 6H).

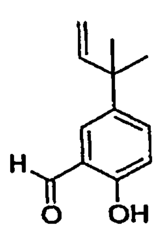
III-019: 2-(2-Dimethylamino-ethoxy)-5-(tetrahydro-pyran-2-yloxy)-benzaldehyde



General procedure E gave the title compound as an yellow oil in 86% yield.

^{1}H NMR ($CDCl_3$) δ 10.46 (s, 1H), 7.50 (d, 1H), 7.27-7.23 (m, 1H), 6.93 (d, 1H), 5.35 (t, 1H), 4.15 (t, 2H), 3.94-3.86 (m, 1H), 3.63-3.57 (m, 2H), 2.77 (t, 2H), 2.35 (s, 6H), 2.01-1.55 (m, 6H).

III-020: 5-(1,1-Dimethyl-allyl)-2-hydroxy-benzaldehyde

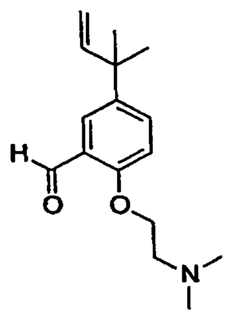


A solution of boron trichloride (1M in CH_2Cl_2, 39.7 mmol) was added dropwise under argon at −78 °C to a stirred solution of 5-(1,1-Dimethyl-allyl)-2-methoxy-benzaldehyde (13.2

mmol) in dry CH_2Cl_2 (120 ml). The dry ice- acetone bath was removed and reaction allowed warming to RT. Stirred at RT for 18 hours, before the reaction mixture was cooled to 0 °C and iced water (125 ml) slowly added. Extracted with CH_2Cl_2 (2 x 100 ml). The organic phases were washed with brine, dried (Na_2SO_4), filtered, and evaporated to black oil. Purified by flash chromatography (heptane:EtOAc) to give the title product as yellow oil in 56% yield.

^{1}H-NMR ($CDCl_3$) δ 10.82 (s, 1H), 9.81 (s, 1H), 7.43 (d, 1H), 7.41 (s, 1H), 6.86 (d, 1H), 5.92 (dd, 1H), 5.02-4.96 (m, 2H), 1.34 (s, 6H).

III-021: 5-(1,1-Dimethyl-allyl)-2-(2-dimethylamino-ethoxy)-benzaldehyde

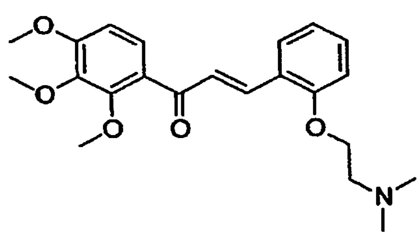


General procedure E gave the title product as yellow oil in 41%) yield.

^{1}H-NMR ($CDCl_3$) δ 10.42 (s, 1H), 7.75 (d, 1H), 7.44 (dd, 1H), 6.85 (d, 1H), 5.96–5.86 (m, 1H), 4.99-4.93 (m, 2H), 4.11 (t, 2H), 2.72 (t, 2H), 2.28 (s, 6H), 1.32 (s, 6H).

Chalcone synthesis

III-022:
(*E*)- 3-[2-(2-Dimethylamino-ethoxy)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone

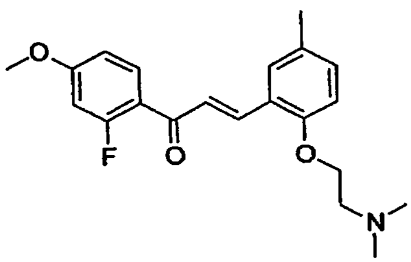


General procedure I gave the title product as yellow oil in 7% yield.

^1H NMR ($CDCl_3$) δ 8.04 (d, 1H), 7,66 (dd, 1H), 7.54 (d, 1H), 7.47 (d, 1H), 7.38 (dd, 1H), 7.00 (t, 1H), 6.94 (d, 1H), 6.77 (d, 1H), 4.16 (t, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.92 (s, 3H), 2.83 (t, 2H), 2.35 (s, 6H).

III-023:

(*E*)- 3-[2-(2-Dimethylamino-ethoxy)-5-methyl-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone



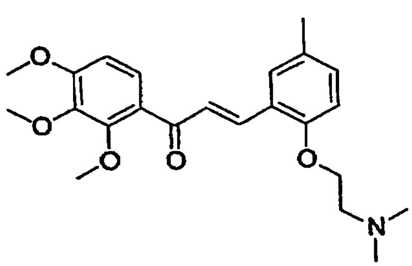
F umarate

General procedure H gave the title product as colourless crystals in 19% yield.

^1H NMR (DMSO-d_6) δ 7.63 (dd, 1H), 7,57 (dd, 1H), 7.36-7.30 (m, 2H), 7.00 (dd, 1H), 6.81-6.67 (m, 3H), 6.36 (s, 2H), 3.92 (t, 2H), 3.63 (s, 3H), 2.56 (t 2H), 2.06 (s, 6H), 2.04 (s, 3H).

III-024:

(*E*)- 3-[2-(2-Dimethylamino-ethoxy)-5-methyl-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone



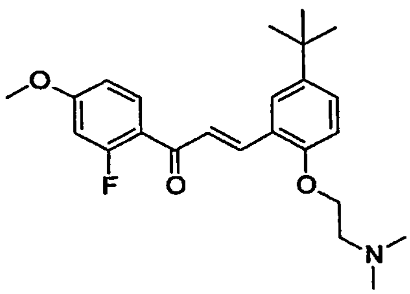
Fumarate

General procedure H gave the title product as yellow crystals in 16% yield.

^{1}H NMR (DMSO-d_6) δ 7.89 (d, 1H), 7,67 (d, 1H), 7.55 (d, 1H), 7.43 (d, 1H), 7.33 (dd, 1H), 7.13 (d, 1H), 7.05 (d, 1H), 6.71 (s, 2H), 4.28 (t, 2H), 3.99 (s, 3H), 3.93 (s, 3H), 3.91 (s, 3H), 2.93 (t, 2H), 2.40 (s, 6H), 2.39 (s, 3H).

III-025:

(*E*)- 3-[5-*tert*-Butyl-2-(2-dimethylamino-ethoxy)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone



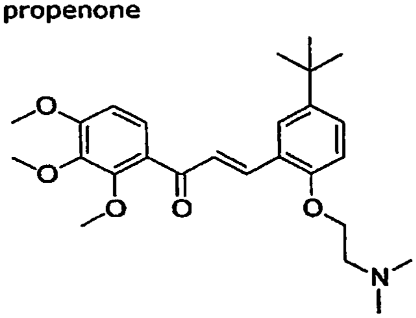
Fumarate

General procedure H gave the title product as yellow crystals in 39% yield.

^{1}H NMR (DMSO-d_6) δ 7.69 (dd, 1H), 7,61 (dd, 1H), 7.52 (dd, 1H), 7.44 (dd, 1H), 7.25 (dd, 1H), 6.86 (d, 1H), 6.81-6.72 (m, 2H), 6.40 (s, 2H), 3.99 (t, 2), 3.68 (s, 3H), 2.63 (t, 2H), 2.12 (s, 6H), 1.10 (s, 9H).

III-026:

(*E*)- 3-[5-*tert*-Butyl-2-(2-dimethylamino-ethoxy)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone



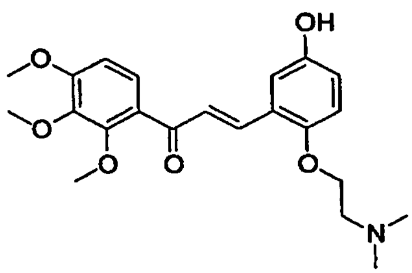
Fumarate

General procedure H gave the title product as yellow crystals in 20% yield.

^{1}H NMR (DMSO-d_6) δ 7.75 (d, 1H), 7.67 (d, 1H), 7.48 (d, 1H), 7.40 (dd, 1H), 7.29 (d, 1H), 7.01 (d, 1H), 6.90 (d, 1H), 6.57 (s, 2H), 4.12 (t, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 3.76 (s, 3H), 2.73 (t, 2H), 2.22 (s, 6H), 1.27 (s, 9H).

III-027:

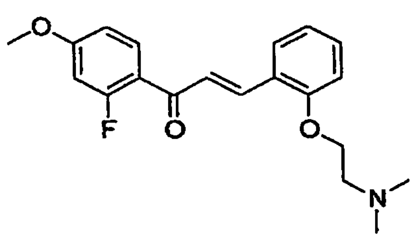
(*E*)- 3-[2-(2-Dimethylamino-ethoxy)-5-hydroxy-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone



General procedure H gave the title product as yellow crystals in 16% yield.

^{1}H NMR (CDCl$_3$) δ 9.18 (bs, 1H), 7.76 (d, 1H), 7.36 (d, 1H), 7.32 (d, 1H), 7.09 (d, 1H), 6.96-6.92 (m, 2H), 6.82 (dd, 1H), 4.02 (t, H), 3.87 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 2.61 (t, 2H), 2.17 (s, 6H).

III-028:
(*E*)- 3-[2-(2-Dimethylamino-ethoxy)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone



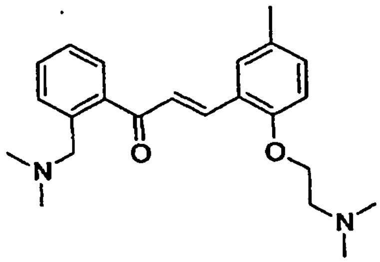
Fumarate

General procedure H gave the title product as yellow crystals in 45% yield.

^{1}H NMR (DMSO-d_6) δ 7.90 (dd, 1H), 7.82-7.76 (m, 2H), 7.59 (dd, 1H), 7.43 (dd, 1H), 714 (d, 1H), 7.05-6.91 (m, 3H), 6.56 (s, 1H), 4.21 (t, 2H), 3.87 (s, 3H), 2.85 (t, 2H), 2.33 (s, 6H).

III-029:

(*E*)- 3-[2-(2-Dimethylamino-ethoxy)-5-methyl-phenyl]-1-(2-dimethylaminomethyl-phenyl)-propenone



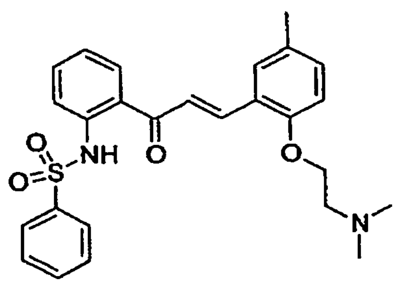
Fumarate

General procedure H gave the title product as yellow crystals in 25% yield.

^{1}H NMR (DMSO-d_6) δ 7.67-7.46 (m, 6H), 7.30 (d, 1H), 7.23 (dd, 1H), 7.00 (d, 1H), 6.58 (s, 4H), 4.20 (t, 2H), 3.70 (s, 2H), 2.95 (t, 2H), 2.38 (s, 6H), 2.27 (s, 3H), 2.23 (s, 6H).

III-030:

(*E*)- N-(2-{3-[2-(2-Dimethylamino-ethoxy)-5-methyl-phenyl]-acryloyl}-phenyl)-benzenesulfonamide

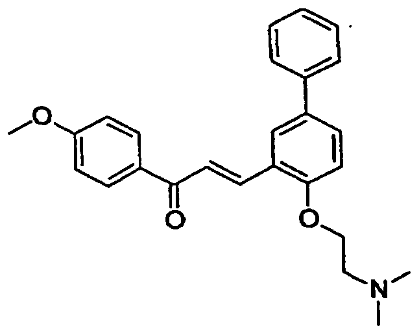


General procedure H gave the title product as yellow crystals in 48% yield.

^{1}H NMR ($CDCl_3$) δ 8.02-7.97 (m, 2H), 7.91-7.88 (m, 2H), 7.79 (dd, 1H), 7.70 (d, 1H), 7.55-7.41 (m, 5H), 7.24 (dd, 1H), 7.18 (dt, 1H) 6.92 (d, 1H), 4.21 (t, 2H), 2.87 (t, 2H), 2.41 (s, 6H), 2.39 (s, 3H).

III-031:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-biphenyl-3-yl]-1-(4-methoxy-phenyl)-propenone



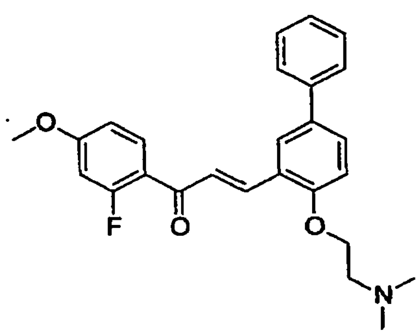
Fumarate

General procedure H gave the title product as yellow crystals in 73% yield.

^{1}H NMR (DMSO-d_6) δ 8.22-8.16 (m, 3H), 8.05 (d, 2H), 7.77-7.71 (m, 3H), 7.47 (t, 2H), 7.35 (t, 1H), 7.23 (d, 1H), 7.09 (d, 2H), 6.58 (s, 2H), 4.31 (t, 2H), 3.87 (s, 3H), 2.99 (t, 2H), 2.45 (s, 6H).

III-032:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-biphenyl-3-yl]-1-(2-fluoro-4-methoxy-phenyl)-propenone



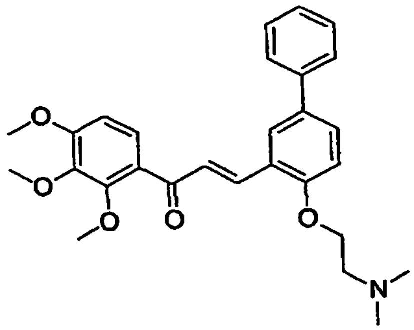
Fumarate

General procedure H gave the title product as yellow crystals in 77% yield.

^{1}H NMR (DMSO-d_6) δ 8.07 (d, 1H), 7.96 (d, 1H), 7.84 (t, 1H), 7.77-7.70 (m, 4H), 7.48 (t, 2H), 7.34 (t, 1H), 7.23 (d, 1H), 7.00-6.91 (m, 2H), 6.58 (s, 2H), 4.30 (t, 2H), 3.87 (s, 3H), 2.96 (t, 2H), 2.41 (s, 6H).

III-033:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-biphenyl-3-yl]-1-(2,3,4-trimethoxy-phenyl)-propenone



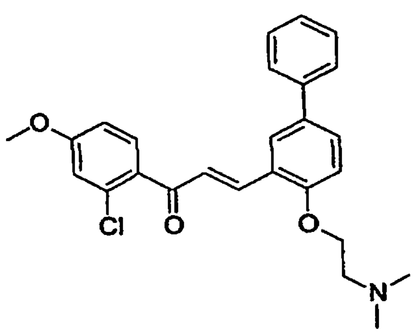
Fumarate

General procedure H gave the title product as colourless crystals in 84% yield.

^{1}H NMR (DMSO-d_6) δ 8.03 (d, 1H), 7.85 (d, 1H), 7.74-7.70 (m, 3H), 7.61 (d, 1H), 7.45 (t, 2H), 7.36-7.30 (m, 2H) 7.22 (d, 1H), 6.94 (d, 1H), 6.58 (s, 2H), 4.27 (t, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 2.92 (t, 2H), 2.36 (s, 6H).

III-034:

(*E*)- 1-(2-Chloro-4-methoxy-phenyl)-3-[4-(2-dimethylamino-ethoxy)-biphenyl-3-yl]-propenone



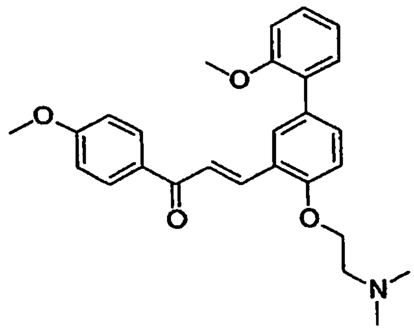
Fumarate

General procedure H gave the title product as slightly yellow crystals in 63% yield.

^{1}H NMR (DMSO-d_6) δ 8.10 (d, 1H), 7.79 (d, 1H), 7.75-7.71 (m, 2H), 7.62 (d, 1H), 7.54 (d, 1H), 7.45 (t, 2H), 7.34 (t, 1H), 7.20 (d, 1H), 7.16 (d, 1H), 7.04 (dd, 1H), 6.57 (s, 2H), 4.26 (t, 2H), 3.86 (s, 3H), 2.91 (t, 2H), 2.35 (t, 6H).

III-035:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-2'-methoxy-biphenyl-3-yl]-1-(4-methoxy-phenyl)-propenone



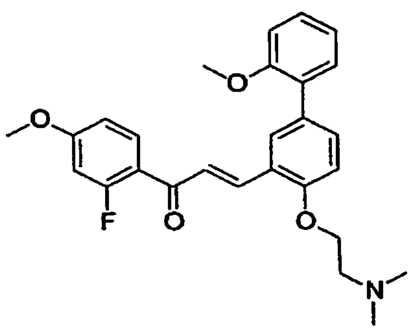
Fumarate

General procedure H gave the title product as slightly yellow crystals in 55% yield.

^{1}H NMR (DMSO-d_6) δ 8.15 (d, 2H), 8.02 (d, 2H), 7.95 (d, 1H), 7.53 (dd, 1H), 7.35 (t, 2H), 7.19-7.01 (m, 5H), 6.58 (s, 1H), 4.26, (t, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 2.86 (t, 2H), 2.36 (s, 6H).

III-036:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-2'-methoxy-biphenyl-3-yl]-1-(2-fluoro-4-methoxy-phenyl)-propenone



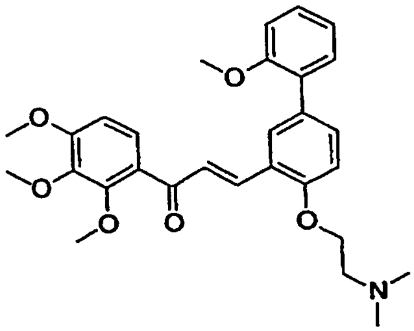
Fumarate

General procedure H gave the title product as yellow crystals in 65% yield.

^{1}H NMR (DMSO-d_6) δ 7.93 (d, 1H), 7.86-7.80 (m, 2H), 7.63 (dd, 1H), 7.55 (dd, 1H), 7.37-7.32 (m, 2H), 7.18 (d, 1H), 7.12 (d, 1H), 7.06-6.91 (m, 3H), 6.59 (s, 2H), 4.27 (t, 2H), 3.87 (s, 3H), 3.78 (s, 3H), 2.90 (t, 2H), 2.36 (s, 6H).

III-037:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-2'-methoxy-biphenyl-3-yl]-1-(2,3,4-trimethoxy-phenyl)-propenone



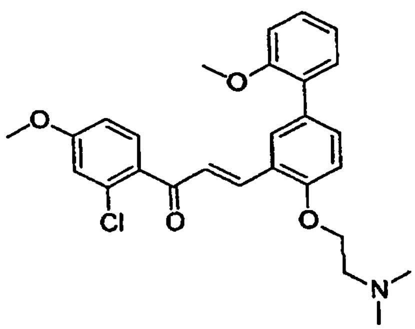
Fumarate

General procedure H gave the title product as slightly yellow crystals in 60% yield.

^{1}H NMR (DMSO-d_6) δ 7.85 (d, 1H), 7.83 (d, 1H), 7.53 (dd, 1H), 7.50 (d, 1H), 7.37-7.31 (m, 3H), 7.17 (d, 1H), 7.11 (d, 1H), 7.03 (t, 1H), 6.93 (d, 1H), 6.59 (s, 3H), 4.28 (t, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 3.78 (s, 3H), 2.96 (t, 2H), 2.40 (s, 6H).

III-038:

(*E*)- 1-(2-Chloro-4-methoxy-phenyl)-3-[4-(2-dimethylamino-ethoxy)-2'-methoxy-biphenyl-3-yl]-propenone



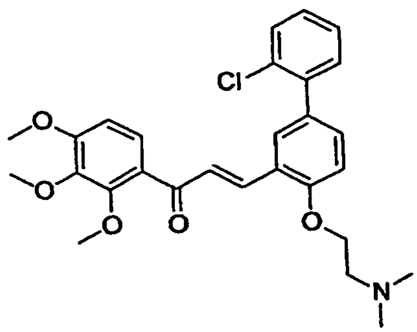
Fumarate

General procedure H gave the title product as slightly yellow crystals in 37% yield.

^{1}H NMR (DMSO-d_6) δ 7.84 (d, 1H), 7.76 (d, 1H), 7.59 (d, 1H), 7.55 (dd, 1H), 7.40 (d, 1H), 7.36-7.31 (m, 2H), 7.16-6.99 (m, 5H), 6.59 (s, 2H), 4.21 (t, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 2.78 (t, 2H), 2.26 (s, 6H).

III-039:

(*E*)- 3-[2'-Chloro-4-(2-dimethylamino-ethoxy)-biphenyl-3-yl]-1-(2,3,4-trimethoxy-phenyl)-propenone



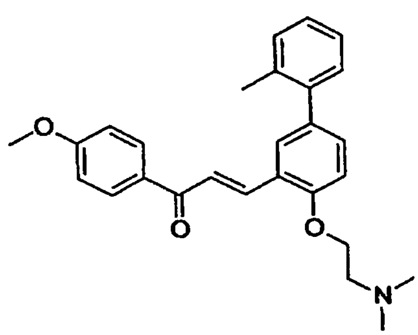
Fumarate

General procedure H gave the title product as colourless crystals in 20% yield.

^{1}H NMR (DMSO-d_6) δ 7.86-7.81 (m, 2H), 7.58-7.39 (m, 6H), 7.35 (d, 1H), 7.22 (d, 1H), 6.93 (d, 1H), 6.59 (s, 2H), 4.26 (t, H), 3.87 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 2.85 (t, 2H), 2.32 (s, 6H).

III-040:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-2'-methyl-biphenyl-3-yl]-1-(4-methoxy-phenyl)-propenone



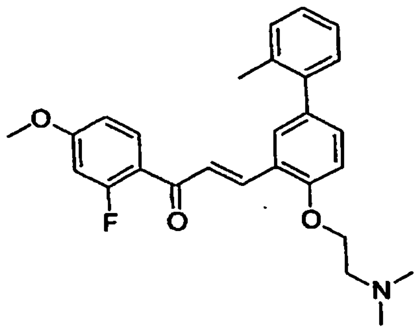
Fumarate

General procedure H gave the title product as Yellow crystals in 76% yield.

^{1}H NMR (DMSO-d_6) δ 8.16 (d, 2H), 8.05 (s, 2H), 7.94 (d, 1H), 7.38 (dd, 1H), 7.33-7.24 (m, 4H), 7.20 (d, 1H), 7.06 (d, 2H) 6.58 (s, 2H), 4.30 (t, 2H), 3.86 (s, 3H), 2.96 (t, 2H), 2.43 (s, 6H), 2.27 (s, 3H).

III-041:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-2'-methyl-biphenyl-3-yl]-1-(2-fluoro-4-methoxy-phenyl)-propenone



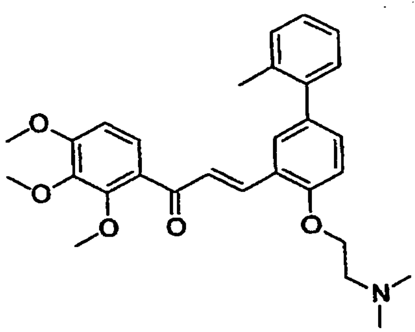
Fumarate

General procedure H gave the title product as slightly yellow crystals in 73% yield.

^1H NMR (DMSO-d_6) δ 7.94 (d, 1H), 7.83 (t, 1H), 7.75 (d, 1H), 7.66 (dd, 1H), 7.40 (dd, 1H), 7.32-7.19 (m, 5H), 6.98-6.89 (m, 2H), 6.58 (s, 2H), 4.29 (t, 2H), 3.86 (s, 3H), 2.94 (t, 2H), 2.39 (s, 6H), 2.26 (s, 3H).

III-042:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-2'-methyl-biphenyl-3-yl]-1-(2,3,4-trimethoxy-phenyl)-propenone



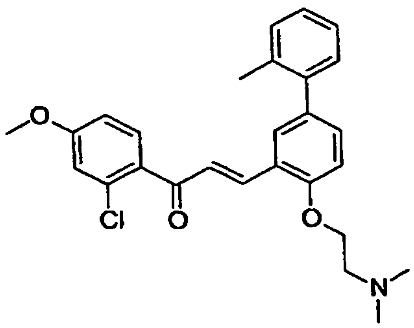
Fumarate

General procedure H gave the title product as slightly yellow crystals in 73% yield.

^1H NMR (DMSO-d_6) δ 7.84 (d, 1H), 7.70 (d, 1H), 7.54 (d, 1H), 7.38 (dd, 1H), 7.34 (d, 1H), 7.30-7.22 (m, 4H), 7.19 (d, 1H, 6.92 (d, 1H), 6.59 (s, 2H), 4.24 (t, 2H), 3.86 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H), 2.83 (t, 2H), 2.30 (s, 6H), 2.26 (s, 3H).

III-043:

(*E*)- 1-(2-Chloro-4-methoxy-phenyl)-3-[4-(2-dimethylamino-ethoxy)-2'-methyl-biphenyl-3-yl]-propenone



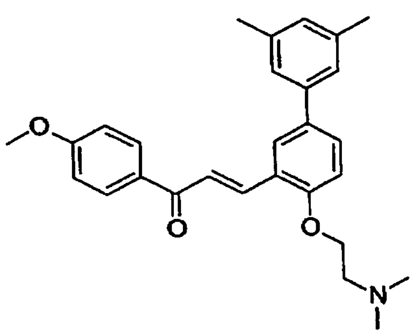
Fumarate

General procedure H gave the title product as yellow crystals in 54% yield.

^{1}H NMR (DMSO-d_6) δ 7.79 (d, 1H), 7.76 (d, 1H), 7.60 (d, 1H), 7.45 (d, 1H), 7.40 (dd, 1H), 7.31-7.14 (m, 6H), 7.03 (dd, 1H), 6.59 (s, 2H), 4.22 (t, 2H), 3.85 (s, 3H), 2.80 (t, 2H), 2.28 (s, 6H), 2.25 (s, 3H).

III-044:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-3',5'-dimethyl-biphenyl-3-yl]-1-(4-methoxy-phenyl)-propenone



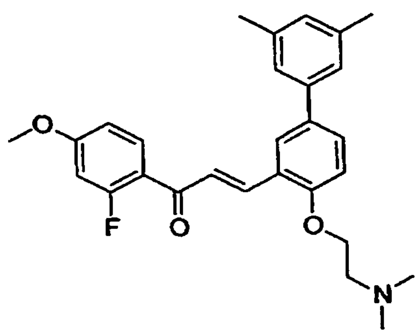
Fumarate

General procedure H gave the title product as slightly yellow crystals in 74% yield.

^{1}H NMR (DMSO-d_6) δ 8.19-8.01 (m, 5H), 7.69 (dd, 1H), 7.34 (bs, 2H), 7.21 (d, 1H), 7.10 (d, 2H), 6.98 (s, 1H), 6.59 (s 2H), 4.29 (t, 2H), 3.87 (s, 3H), 2.94 (t, 2H), 2.42 (s, 6H), 2.35 (s, 6H).

III-045:

(E)- 3-[4-(2-Dimethylamino-ethoxy)-3',5'-dimethyl-biphenyl-3-yl]-1-(2-fluoro-4-methoxy-phenyl)-propenone



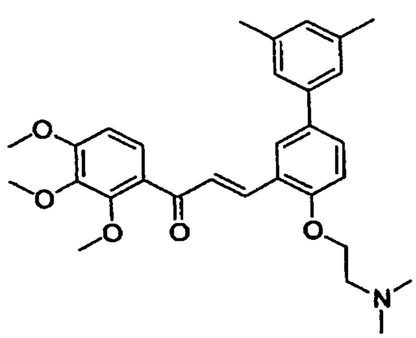
Fumarate

General procedure H gave the title product as yellow crystals in 73% yield.

^{1}H NMR (DMSO-d_6) δ 8.02 (d, 1H), 7.93 (d, 1H), 7.83 (t, 1H), 7.73 (dd, 1H), 7.69 (t, 1H), 7.31 (bs, 2H), 7.20 (d, 1H), 7.00-6.91 (m, 3H), 6.59 (s, 2H), 4.27 (t, 2H), 3.87 (s, 3H), 2.90 (t, 2H), 2.36 (s, 6H), 2.33 (s, 6H).

III-046:

(E)- 3-[4-(2-Dimethylamino-ethoxy)-3',5'-dimethyl-biphenyl-3-yl]-1-(2,3,4-trimethoxy-phenyl)-propenone



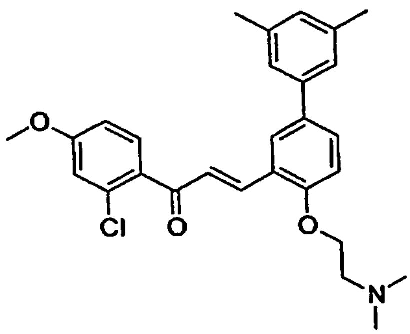
Fumarate

General procedure H gave the title product as yellow crystals in 52% yield.

^{1}H NMR (DMSO-d_6) δ 7.99 (d, 1H), 7.83 (d, 1H), 7.68 (dd, 1H), 7.59 (d, 1H), 7.34 (d, 1H), 7.30 (bs, 2H), 7.19 (d, 1H), 696 (bs, 1H), 6.93 (d, 1H), 6.58 (s, 2H), 4.27 (t, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 2.93 (t, 2H), 2.38 (s, 6H), 2.33 (s, 6H).

III-047:

1-(2-Chloro-4-methoxy-phenyl)-3-[4-(2-dimethylamino-ethoxy)-3',5'-dimethyl-biphenyl-3-yl]-propenone



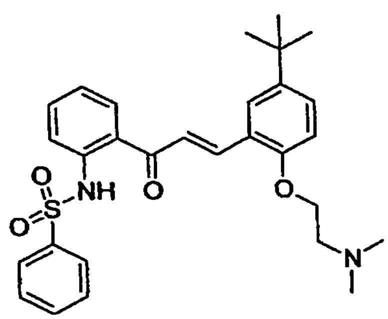
Fumarate

General procedure H gave the title product as yellow crystals in 77% yield.

^{1}H NMR (DMSO-d_6) δ 8.05 (d, 1H), 7.76 (d, 1H), 7.71 (dd, 1H), 7.60 (d, 1H), 7.51 (d, 1H), 7.32 (bs, 2H), 7.18 (d, 1H) 7.16 (d, 1H), 7.05 (dd, 1H), 6.96 (bs, 1H), 6.59 (s, 2H), 4.22 (t, 2H), 3.86 (s, 3H), 2.82 (t, 2H), 2.33 (s, 6H), 2.29 (s, 6H).

III-048:

(*E*)- N-(2-{3-[5-*tert*-Butyl-2-(2-dimethylamino-ethoxy)-phenyl]-acryloyl}-phenyl)-benzenesulfonamide

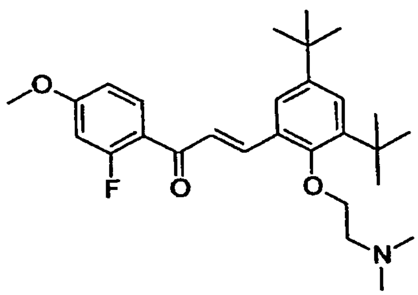


General procedure H gave the title product as yellow crystals in 33% yield.

^{1}H-NMR (CDCl$_3$) δ 7.97 (dd, 1H), 7.93 (d, 1H), 7.87-7.84 (m, 2H), 7.76 (dd, 1H), 7.73 (d, 1H), 7.54 (d, 1H), 7.51-7.37 (m, 5H), 7.14 (m, 1H), 6.92 (d, 1H), 4.18 (t, 2H) 2.82 (t, 2H), 2.36 (s, 6H), 1.35 (s, 9H).

III-049:

(E)- 3-[3,5-Di-*tert*-butyl-2-(2-dimethylamino-ethoxy)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone

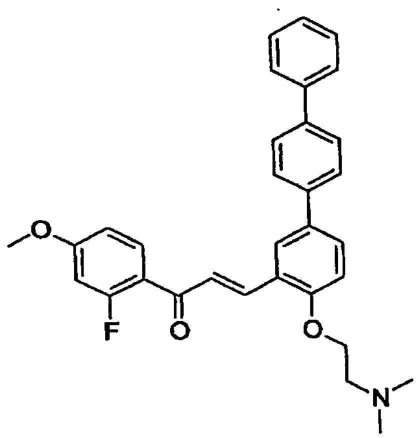


General procedure H gave the title product as yellow crystals in 11% yield.

^{1}H NMR ($CDCl_3$) δ 7.97 (dd, 1H), 7,79 (dd, 1H), 7.42 (d, 1H), 7.35 (d, 1H), 7.30 (dd, H), 6.72 (dd, 1H), 6.60 (dd, 1H), 3.85, (t, 2H), 3.81 (s, 3H), 2.72 (t, 2H), 2.24 (s, 6H), 1.34 (s, 9H), 1.26 (s, 9H).

III-050:

(E)- 3-[4-(2-Dimethylamino-ethoxy)-[1,1';4',1"]terphenyl-3-yl]-1-(2-fluoro-4-methoxy-phenyl)-propenone

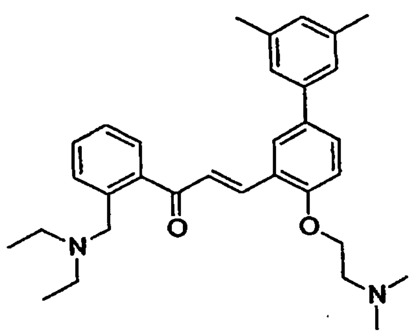


General procedure H gave the title product as yellow crystals in 23% yield.

^1H NMR ($CDCl_3$) δ 8.06 (dd, 1H), 7,86-7.80 (m, 2H), 7.63-7.54 (m, 4H), 7.39 (dd, 2H),7.31 (s, 1H), 6.96 (d, 1H), 6.72 (dd, 1H), 6.59 (dd, 1H), 4.15 (t, 2H), 3.81, (s, 3H), 2.80 (d, 2H), 2.30 (s, 6H).

III-051:

(*E*)- 1-(2-Diethylaminomethyl-phenyl)-3-[4-(2-dimethylamino-ethoxy)-3',5'-dimethyl-biphenyl-3-yl]-propenone



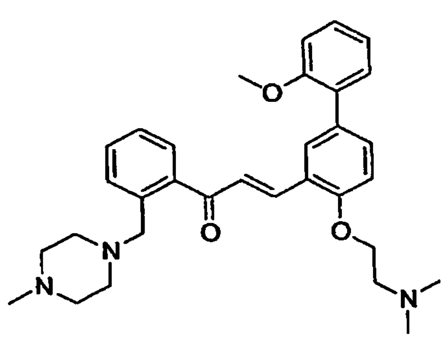
Fumarate

General procedure H gave the title product as green crystals in 33% yield.

^1H-NMR (DMSO-d_6) δ 8.02 (d, 1H), 7.67 (dd, 1H), 7.61 (d, 1H), 7.47-7.38 (m 4H), 7.37 (d, 1H), 7.31 (br, 2H), 7.15 (d, 1H) 6.96 (br, 1H), 6.59 (s, 3H) 4.19 (t, 2H), 3.68 (s, 2H), 2.78 (t, 2H), 2.40 (q, 4H), 2.39 (s, 6H), 2.24 (s, 6H), 0.86 (t, 6H).

III-052:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-2'-methoxy-biphenyl-3-yl]-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone



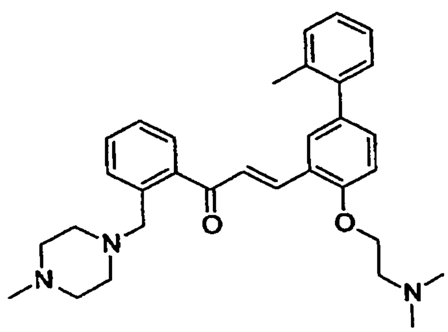
Fumarate

General procedure H gave the title product as yellow crystals in 40% yield.

¹H-NMR (DMSO-d_6) δ 7.85 (d, 1H), 7.59 (d, 1H), 7.56-7.33 (m, 7H), 7.25 (d, 1H), 7.16-7.12 (dd, 2H), 7.04 (t, 1H), 6.61 (s, H), 4.22 (t, 2H), 3.79 (s, 3H), 3.60 (s, 2H), 2.81 (t, 2H), 2.50-2.30 (broad, 8H), 2.28 (s, 6H), 2.22 (s, 3H).

III-053:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-2'-methyl-biphenyl-3-yl]-1-[2-(4-methyl-piperazin-1-ylmethyl)-phenyl]-propenone

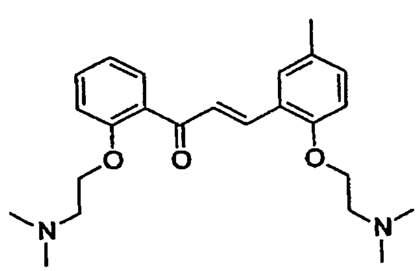


General procedure H gave the title product as yellow crystals in 39% yield.

¹H-NMR ($CDCl_3$) δ 7.63 (d, 1H), 7.55 (d, 1H), 7.41-7.24 (m, 9H), 7.10 (d, 1H), 6.96 (d, 1H), 4.15 (t, 2H), 3.61 (s, 2H), 2.73 (t, 2H), 2.40 (bs, 8H), 2.30 (s, 3H), 2.27 (s, 6H), 2.18 (s, 3H).

III-054:

(*E*)- 3-[2-(2-Dimethylamino-ethoxy)-5-methyl-phenyl]-1-[2-(2-dimethylamino-ethoxy)-phenyl]-propenone



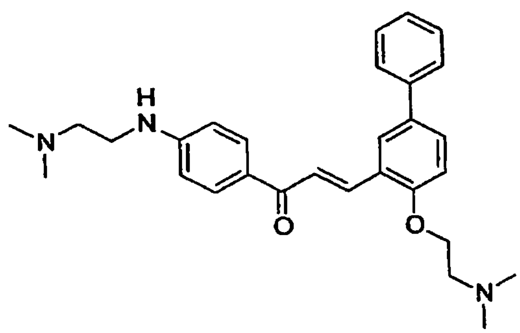
Fumarate

General procedure H gave the title product as colourless crystals in 15% yield.

^1H NMR (DMSO-d_6) δ 7.79 (d, 1H), 7,59 (d, 1H), 7.55-.42 (m, 3H), 7.24-7.19 (m, 2H), 7.06 (dd, 1H), 7.00 (d, 1H), 6.58 (s, 4H), 4.23 (t, 2H), 4.15 (t, 2H), 2.84 (t, 2H), 2.80 (t, 2H), 2.33 (s, 6H), 2.27 (s, 3H), 2.26 (s, 6H).

III-055:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-biphenyl-3-yl]-1-[4-(2-dimethylamino-ethylamino)-phenyl]-propenone



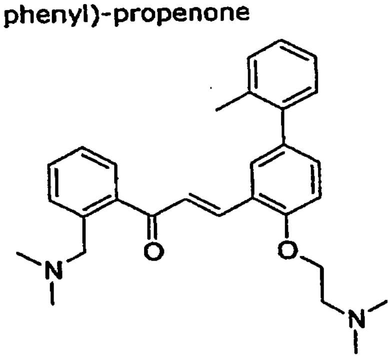
Fumarate

General procedure H gave the title product as yellow crystals in 14% yield.

^1H NMR (DMSO-d_6) δ 8.16 (d, 1H), 8.08 (d, 1H), 8.01 (d, 2H), 7.96 (d, 1H), 7.75 (d, 2H), 7.70 (dd, 1H), 7.47 (dd, 2H), 7.35 (dd, 1H), 7.23 (d, 1H), 6.69 (d, 2H), 6.58 (s, 2H), 4.28 (t, 1H), 3.32 (dt, 2H), 2.89 (t, 2H), 2.70 (t, 2H), 2.38 (s, 6H).

III-056:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-2'-methyl-biphenyl-3-yl]-1-(2-dimethylaminomethyl-phenyl)-propenone

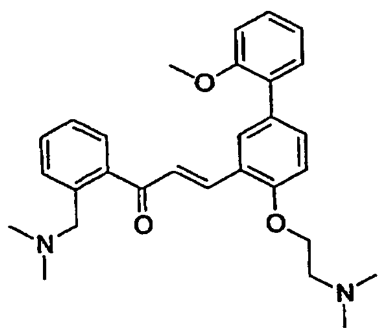


Fumarate

General procedure H gave the title compound as pale green crystals in 28% yield.

^{1}H-NMR (DMSO-d_6) δ 7.79 (d, 1H), 7.69 (d, 1H), 7.55-7.37 (m, 5H), 7.28-7.22 (m, 5H), 7.16 (d, 1H), 6.59 (s, 4H), 4.24 (t, 2H), 3.67 (s, 2H), 2.87 (t, 2H), 2.32 (s, 6H), 2.26 (s, 3H), 2.17 (s, 6H).

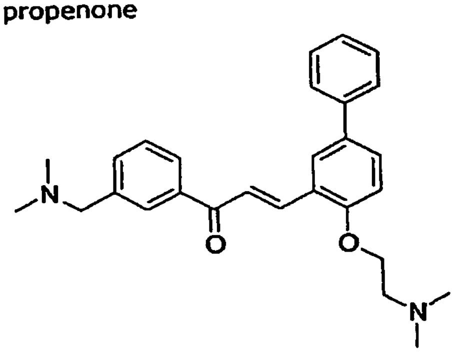
III-057:
(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-2'-methoxy-biphenyl-3-yl]-1-(2-dimethylaminomethyl-phenyl)-propenone


Fumarate

General procedure H gave the title compound as pale green crystals in 29% yield.

^{1}H-NMR (DMSO-d_6) δ 7.86 (d, 1H), 7.68 (d, 1H), 7.55-7.43 (m, 5H), 7.37-7.31 (m, 3H), 7.12 (t, 2H), 7.05 (t, 1H), 6.58 (s, 4H), 4.25 (t, 2H),, 3.76 (s, 3H) 3.68 (s, 2H), 2.91 (t, 2H), 2.34 (s, 6H), 2.19 (s, 6H).

III-058:
(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-biphenyl-3-yl]-1-(3-dimethylaminomethyl-phenyl)-propenone

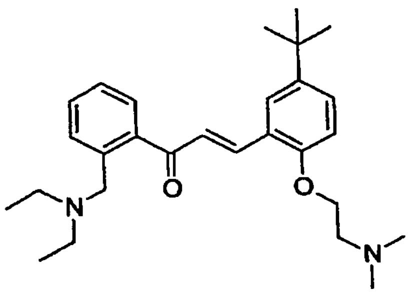


General procedure H gave the title compound as yellow oil in 42% yield.

^1H NMR ($CDCl_3$) δ 8.07 (d, 1H), 7.90-7.88 (m, 2H), 7.77 (d, 1H), 7.71 (d, 1H), 7.54-7.47 (m, 4H), 7.41-7.38 (m, 3H), 7.36-7.25 (m, 1H), 6.96 (d, 1H), 4.15 (t, 2H), 3.44 (s, 2H), 2.80 (t, 2H), 2.31 (s, 6H), 2.20 (s, 6H).

III-059:

(*E*)- 3-[5-*tert*-Butyl-2-(2-dimethylamino-ethoxy)-phenyl]-1-(2-diethylaminomethyl-phenyl)-propenone

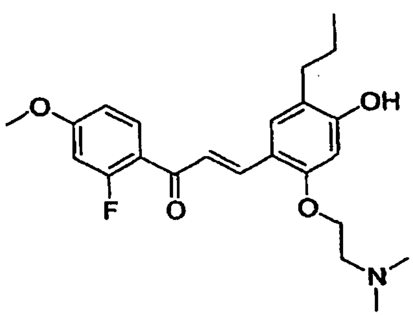


General procedure H gave the title compound as a green oil in 42% yield.

^1H-NMR (DMSO-d_6) δ 7.68 (d, 1H), 7.52 (d, 1H), 7.43-7.32 (m, 5H), 7.20 (d, 1H), 6.98 (d, 1H), 4.04 (t, 2H), 3.59 (s, 2H), 2.54 (t (under DMSO), 2H), 2.33 (q, 4H), 2.08 (s, 6H), 1.28 (s, 9H), 0.82 (t, 6H).

III-060:

(*E*)- 3-[2-(2-Dimethylamino-ethoxy)-4-hydroxy-5-propyl-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone



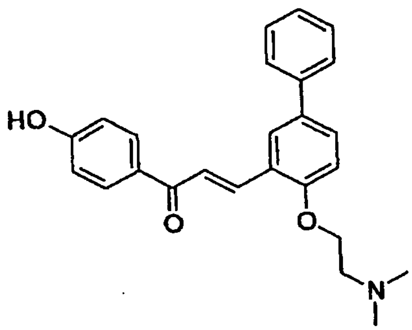
Fumarate

General procedure H gave the title compound as yellow crystals in 14% yield.

^1H-NMR (DMSO-d_6) δ 7,74-7,60 (m, 2H); 7,36-7,25 (m, 2H); 6,86-6,78 (m; 2H); 6,48-6,41 (m, 2H); 3,97 (t, 2H); 3,75 (s, 3H); 2,66 (t, 2H); 2,40-2,32 (m, 3H); 2,17 (s, 6H); 1,46-1,39 (m, 2H); 0,81-0,76 (t, 2H).

III-061:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-biphenyl-3-yl]-1-(4-hydroxy-phenyl)-propenone

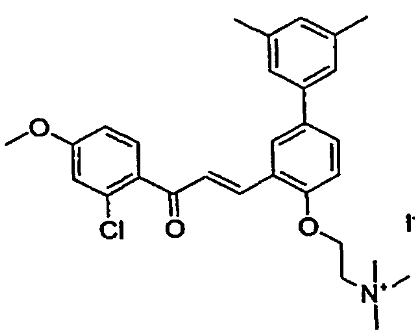


General procedure H gave the title compound as yellow crystals in 25% yield.

^{1}H NMR ($CDCl_3$) δ 7.99 (d, 1H), 7.93 (d, 1H), 7.76 (d, 1H), 7.73 (s, 1H), 7.52-7.47 (m, 3H), 7.36 (t, 2H), 7.28-7.23 (m, 1H), 6.95 (d, 1H), 6.84 (dd, 2H), 4.14 (t, 2H), 2.79 (t, 2H), 2.31 (s, 6H).

III-062:

(*E*)- (2-{3-[3-(2-Chloro-4-methoxy-phenyl)-3-oxo-propenyl]-3',5'-dimethyl-biphenyl-4-yloxy}-ethyl)-trimethyl-ammonium; iodide

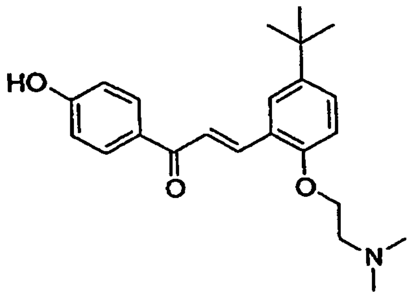


General procedure J gave the title compound as yellow crystals in 33% yield.

^{1}H NMR (DMSO-d_6) δ 8.14 (d, 1H), 7.79 (dd, 1H), 7.78 (d, 1H), 7.64 (d, 1H), 7.51 (d, 1H), 7.34 (s, 2H), 7.25 (d, 1H), 7.17 (d, 1H), 7.06 (dd, 1H), 7.00 (s, 1H), 4.60 (b, 2H), 3.88 (m, 5 H), 3.17 (s, 9H), 2.34 (s., 6H).

III-063:

(*E*)- 3-[5-*tert*-Butyl-2-(2-dimethylamino-ethoxy)-phenyl]-1-(4-hydroxy-phenyl)-propenone



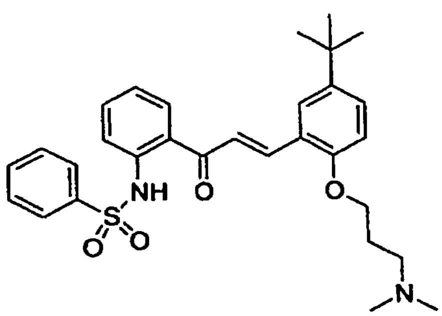
Fumarate

General procedure H gave the title compound as yellow crystals in 47% yield.

^{1}H NMR (DMSO-d_6) 8.05 (d, 2H), 7.95 (s, 2H), 7.82 (d, 1H), 7.42 (d, 1H), 7.05 (d, 1H), 6.91 (d, 2H), 6.58 (s, 3H), 4.24 (t, 2H), 3.00 (t, 2H), 2.46 (s, 6H), 1.32 (s, 9H).

III-064:

(*E*)- N-(2-{3-[5-*tert*-Butyl-2-(3-dimethylamino-propoxy)-phenyl]-acryloyl}-phenyl)-benzenesulfonamide

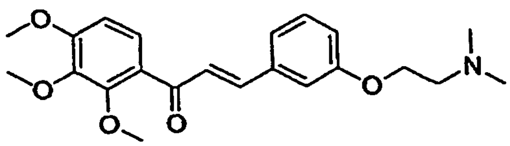


General procedure H gave the title compound as yellow crystals in 27% yield.

^{1}H-NMR ($CDCl_3$) δ 7.94 (d, 1H), 7.89-7.83 (m, 3H), 7.76 (dd, 1H), 7.56 (d, 1H), 7.4 (d, 1H), 7.52-7.37 (m, 5H), 7.17-7.12 (m, 1H), 6.92 (d, 1H), 4.14 (t, 2H) 2.50 (t, 2H), 2.26 (s, 6H), 2.06 (pen, 1H), 1.35 (s, 9H).

III-065:

(*E*)- 3-[3-(2-Dimethylamino-ethoxy)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone



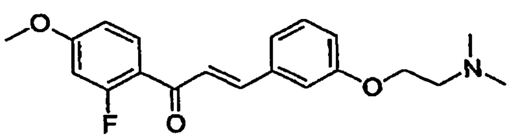
Fumarate

General procedure H gave the title compound as slightly yellow crystals in 9% yield.

^{1}H NMR (DMSO-d_6) δ 7.39 (d, 1H), 7.33-7.27 (m, 2H), 7.19-7.14 (m, 2H), 7.09 (bs, 1H), 7.00 (dd, 1H), 6.80 (d, 1H), 6.59 (s, 2H), 4.29 (t, 2H), 382 (s, 3H), 3.76 (s, 3H), 3.73 (s, 3H), 3.53 (t, 2H), 2.91 (s, 6H).

III-066:

(*E*)- 3-[3-(2-Dimethylamino-ethoxy)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone



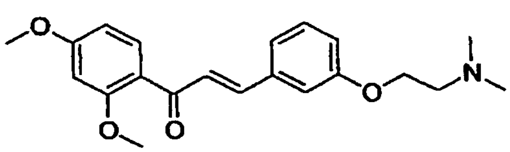
Fumarate

General procedure H gave the title compound as slightly yellow crystals in 24% yield.

^{1}H NMR (DMSO-d_6) δ 7.85 (t, 1H), 7.63 (d, 1H), 7.52 (dd, 1H), 7.38-7.35 (m, 3H), 7.06-6.92 (m,3H), 6.57(s, 2H), 4.20 (t, 2H), 3.87 (s, 3H), 2.51 (t, 2H), 2.41 (s, 6H).

III-067:

(*E*)- 1-(2,4-Dimethoxy-phenyl)-3-[3-(2-dimethylamino-ethoxy)-phenyl]-propenone



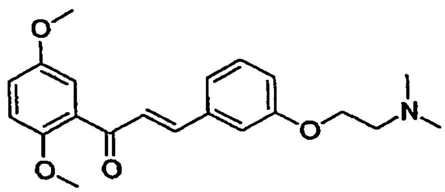
Fumarate

General procedure H gave the title compound as slightly yellow crystals in 24% yield.

^{1}H NMR (DMSO-d6) δ 7.61 (d, 1H), 7.55 (d, 1H), 7.49 (d, 1H), 7.39-7.29 (m, 3H), 7.02 (dt, 1H), 6.69 (d, 1H), 6.65 (dd, 1H), 6.57 (s, 2H), 4.20 (t, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 2.92 (t, 2H), 2.42 (s, 6H).

III-068:

(*E*)- 1-(2,5-Dimethoxy-phenyl)-3-[3-(2-dimethylamino-ethoxy)-phenyl]-propenone



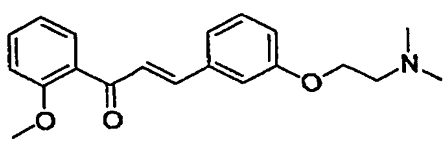
Fumarate

General procedure H gave the title compound as yellow crystals in 33% yield.

^{1}H NMR (DMSO-d_6) δ 7.32 (d, 1H), 7.24 (d, 1H), 7.19-7.13 (m, 3H), 7.01-6.94 (m, 2H), 6.88-6.84 (m, 2H), 6.42 (s, 2H), 4.01 (t, 2H), 3.65 (s, 3H), 3.59 (s, 3H), 2.67 (t, 2H), 2.20 (s, 6H).

III-069:

(*E*)- 3-[3-(2-Dimethylamino-ethoxy)-phenyl]-1-(2-methoxy-phenyl)-propenone



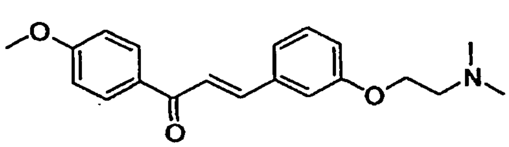
Fumarate

General procedure H gave the title compound as colourless crystals in 20% yield.

^{1}H NMR (DMSO-d_6) δ 7.55 (dt, 1H), 7.49 (dd, 1H), 7.44 (d, 2H), 7.38 (m, 3H), 7.20 (d, 1H), 7.09-7.00 (m, 2H), 4.57 (s, 2H), 4.19 (t, 2H), 3.86 (s, 3H), 2.91 (t, 2H), 2.42 (s, 6H).

III-070:

(*E*)- 3-[3-(2-Dimethylamino-ethoxy)-phenyl]-1-(4-methoxy-phenyl)-propenone



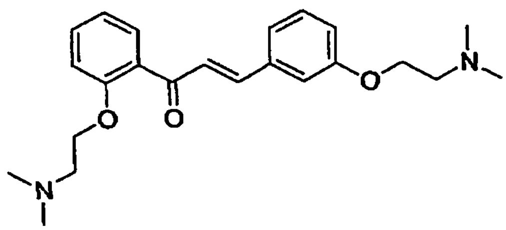
Fumarate

General procedure H gave the title compound as slightly yellow crystals in 10% yield.

^{1}H NMR (DMSO-d_6) δ 8.39 (d, 2H), 8.17 (d, 1H), 7.89 (d, 1H), 7.72-7.55 (m, 3H), 7.32-7.23 (m, 3H), 6.78 (s, 2), 4.46 (t, 2H), 4.09 (s, 3H), 3.18 (t, 2H), 2.67 (s, 6H).

III-071:

(*E*)- 3-[3-(2-Dimethylamino-ethoxy)-phenyl]-1-[2-(2-dimethylamino-ethoxy)-phenyl]-propenone

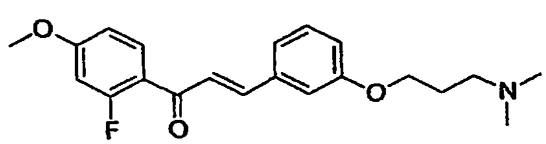


General procedure H gave the title compound as an yellow oil in 25% yield.

^{1}H NMR ($CDCl_3$) δ 7.65 (dd, 1H), 7.60 (d, 1H), 7.47 (d, 1H), 7.47 (dt, 1H), 7.31 (t, 1H), 7.22 (d, 1H), 7.1 (t, 1H), 7.05 (dt, 1H), 7.02 (m, 2H), 4.17 (t, 2H), 4.10 (t, 2H), 2.75 (t, 2H), 2.73 (t, 2H), 2.36 (s, 3H), 2.27 (s, 3H).

III-072:

(*E*)- 3-[3-(3-Dimethylamino-propoxy)-phenyl]-1-(2-fluoro-4-methoxy-phenyl)-propenone

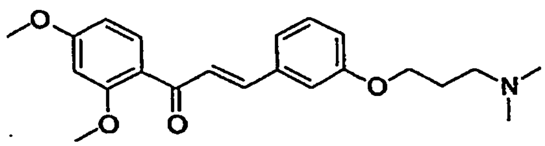


General procedure H gave the title compound as an yellow oil in 32% yield.

^{1}H NMR ($CDCl_3$) δ 7.90 (t, 1H), 7.75 (dd, 1H), 7.44 (dd, 1H), 7.32 (t, 1H), 7.22 (d, 1H), 7.17 (bs, 1H), 6.7 (dd, 1H), 6.81 (dd, 1H), 6.67 (dd, 1H), 4.07 (t, 2H), 3.89 (s, 3H), 2.48 (t, 2H), 2.28 (s, 6H), 1.99 (hep, 2H).

III-073:

(*E*)- 1-(2,4-Dimethoxy-phenyl)-3-[3-(3-dimethylamino-propoxy)-phenyl]-propenone

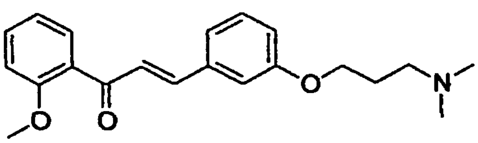


General procedure H gave the title compound as an yellow oil in 52% yield.

^{1}H NMR ($CDCl_3$) δ 7.77 (d, 1H), 7.65 (d, 1H), 7.49 (d, 1H), 7.30 (t, 1H), 7.20 (d, 1H), 7.13 (t, 1H), 6.4 (dd, 1H), 6.58 (dd, 1H), 6.52 (d, 1H), 4.06 (t, 2H), 3.92 (s, 3H), 3.89 (s, 3H), 2.47 (t, 2H), 2.27 (s, 6H), 1.98 (hep, 2H).

III-074:

(*E*)- 3-[3-(3-Dimethylamino-propoxy)-phenyl]-1-(2-methoxy-phenyl)-propenone

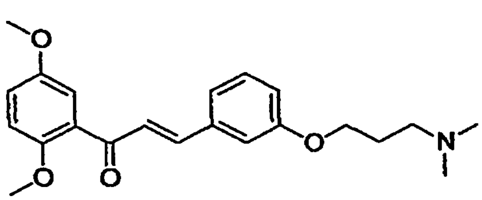


General procedure H gave the title compound as an yellow oil in 41% yield.

^{1}H NMR ($CDCl_3$) δ 7.62 (dd, 1H), 7.58 (d, 1H), 7.50 (dt, 1H), 7.35 (d, 1H), 7.31 (t, 1H), 7.19 (d, 1H), 7.12 (t, 1H), 7.07 (dd, 1H), 7.02 (d, 1H), 6.96 (dd, 1H), 4.06 (t, 2H), 3.92 (s, 3H), 2.47 (t, 2H), 2.27 (s, 6H), 1.98 (hep, 2H).

III-075:

(*E*)- 1-(2,5-Dimethoxy-phenyl)-3-[3-(3-dimethylamino-propoxy)-phenyl]-propenone

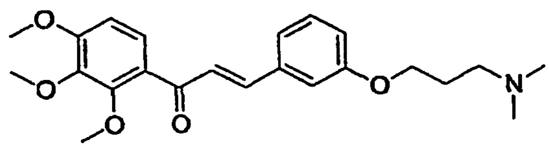


General procedure H gave the title compound as an yellow oil in 28% yield.

^{1}H NMR ($CDCl_3$) δ 7.58 (d, 1H), 7.36 (d, 1H), 7.28 (t, 1H), 7.17-7.15 (m, 2H), 7.10 (t, 1H), 7.02 (dd, 1H),6.94 (d, 2H), 4.04 (t, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 2.45 (t, 2H), 2.25 (s, 6H), 2.04 (hep, 2H).

III-076:

(*E*)- 3-[3-(3-Dimethylamino-propoxy)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone

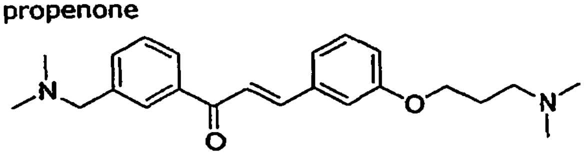


General procedure H gave the title compound as an yellow oil in 21% yield.

^{1}H NMR ($CDCl_3$) δ 7.65 (d, 1H), 7.50 (d, 1H), 7.47 (d, 1H), 7.31 (t, 1H), 7.20 (d, 1H), 7.15 (t, 1H), 6.5 (dd, 1H), 6.77 (d, 1H), 4.06 (t, 2H), 3.94 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 2.47 (t, 2H), 2.27 (s, 6H), 1.98 (hep, 2H).

III-077:

(*E*)- 1-(3-Dimethylaminomethyl-phenyl)-3-[3-(3-dimethylamino-propoxy)-phenyl]-propenone

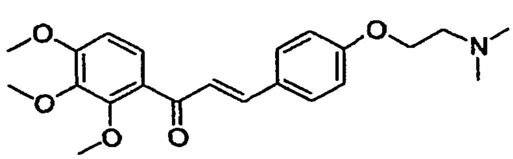


General procedure H gave the title compound as yellow oil in 38% yield.

^{1}H NMR ($CDCl_3$) δ 7.97-7.92 (m, 2H), 7.79 (d, 1H), 7.59-7.57 (m, 2H), 7.49 (t, 1H), 7.34 (t, H), 7.26-7.20 (m, 2H), 6.98 (dd, 1H), 4.09 (t, 2H), 3.53 (s, 2H), 2.51 (t, 2H), 2.30 (s, 6H), 2.29 (s, 6H), 2.01 (m, 2H).

III-078:

(*E*)- 3-[4-(2-Dimethylamino-ethoxy)-phenyl]-1-(2,3,4-trimethoxy-phenyl)-propenone



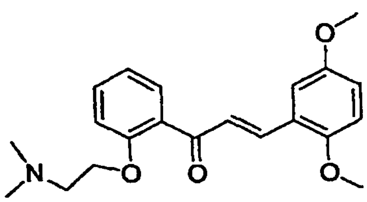
Fumarate

General procedure H gave the title compound as slightly yellow crystals in 22% yield.

^{1}H NMR (DMSO-d_6) δ 7.69 (d, 2H), 7.51 (d, 1H), 7.36-7.29 (m, 2H), 7.01 (d, 2H), 6.92 (d, 1H), 6.57 (s, 2H), 4.19 (t, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 379 (s, 3H), 2.89 (t, 2H), 2.40 (s, 6H).

III-079:

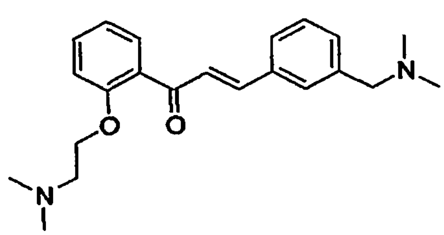
(*E*)- 3-(2,5-Dimethoxy-phenyl)-1-[2-(2-dimethylamino-ethoxy)-phenyl]-propenone



General procedure H gave the title compound as an yellow-brown oil in 18% yield.

^{1}H NMR ($CDCl_3$) δ 7.93 (d, 1H), 7.62 (dd, 1H), 7.47-7.41 (m, 2H), 7.17 (d, 1H), 7.04 (dt, 1H), 6.99 dd, 1H), 6.90 (d, 1H), 6.84 (d, 1H), 4.17 (t, 2H), 3.83 (s, 3H), 3.80 (s, 3H), 2.74 (t, 2H), 2.27 (s, 6H).

III-080:
(*E*)- 1-[2-(2-Dimethylamino-ethoxy)-phenyl]-3-(3-dimethylaminomethyl-phenyl)-propenone

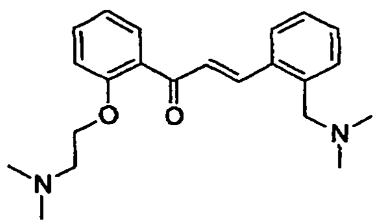


Fumarate

General procedure H gave the title compound as yellow crystals in 32% yield.

^{1}H-NMR ($CDCl_3$) δ 7.73-7.70 (m, 2H), 7.62-7.43 (m, 6H), 7.23 (d, 1H), 7.09 (t, 1H), 6.60 (s, 4H), 4.27 (t, 2H), 3.63 (s, 2H), 2.83 (t, 2H), 2.29 (s, 12H).

III-081:
(*E*)- 1-[2-(2-Dimethylamino-ethoxy)-phenyl]-3-(2-dimethylaminomethyl-phenyl)-propenone

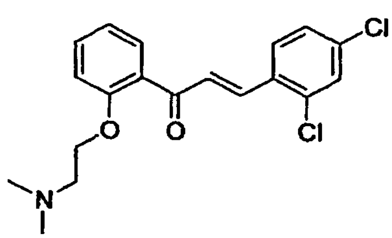


General procedure H gave the title compound as brown oil in 20% yield.

^{1}H-NMR ($CDCl_3$) δ 8.10 (d, 1H), 7.77-7.74 (m, 1H), 7.63 (dd, 1H), 7.47-7.27 (m, 5H), 7.06-6.97 (m, 2H), 4.15 (t, 2H), 3.47 (s, 2H), 2.71 (t, 2H), 2.25 (s, 6H), 2.19 (s, 6H).

III-082:

(*E*)- 3-(2,4-Dichloro-phenyl)-1-[2-(2-dimethylamino-ethoxy)-phenyl]-propenone

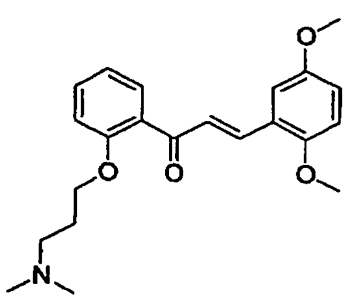


General procedure H gave the title compound as yellow crystals in 9% yield.

^{1}H NMR ($CDCl_3$) δ 8.00 (d, 1H), 7.77 (d, 1H), 7.72 (dd, 1H), 7.57 (d, 1H), 7.50 (dt, 1H), 7.47 (d,1H), 7.30-7.26 (m, 1H), 7.07 (dt, 1H), 7.01 (d, 1H), 4.19 (t, 2H), 2.73 (t, 2H), 2.28 (s, 6H).

III-083:

(*E*)- 3-(2,5-Dimethoxy-phenyl)-1-[2-(3-dimethylamino-propoxy)-phenyl]-propenone

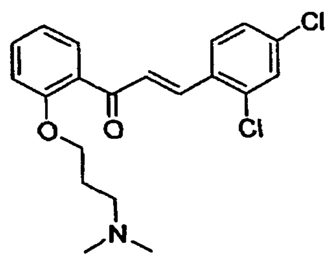


General procedure H gave the title compound as an yellow oil in 58% yield.

^{1}H NMR (CDCl$_3$) δ 7.56 (d, 1H), 7.33-7.22 (m, 3H), 7.08 (d, 1H), 6.94 (d, 1H), 6.85-6.76 (m, 3H), 3.88 (t, H), 3.58 (s, 3H), 3.54 (s, 3H), 2.29 (t, 2H), 1.74 (s, 6H), 1.59 (hep, 2H).

III-084:

(*E*)- 3-(2,4-Dichloro-phenyl)-1-[2-(3-dimethylamino-propoxy)-phenyl]-propenone

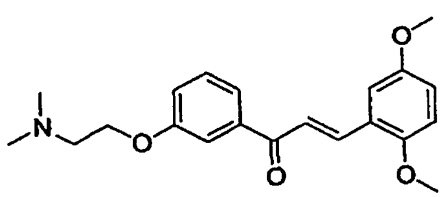


General procedure H gave the title compound as an orange oil in 34% yield.

^{1}H NMR (CDCl$_3$) δ 7.96 (d, 1H), 7.66 (dd, 1H), 7.65 (d, 1H), 7.51 (m, 2H), 7.41 (d, 1H), 7.28 (dd, 1H), 7.07-6.99 (m, 2H), 4.13 (t, 2H), 2.37 (t, 2H), 2.14 (s, 6H), 1.94 (hep, 2H).

III-085:

(*E*)- 3-(2,5-Dimethoxy-phenyl)-1-[3-(2-dimethylamino-ethoxy)-phenyl]-propenone

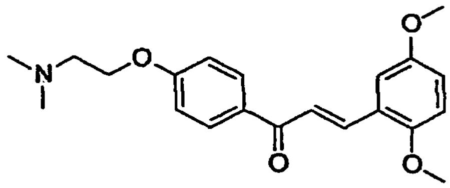


General procedure I gave the title compound as an yellow oil in 6% yield.

^{1}H NMR (CDCl$_3$) δ 8.08 (d, 1H), 7.60-7.53 (m, 3H), 7.39 (t, 1H), 7.17 (d, 1H), 7.15 (dd, 1H), 6.94 (dd, 1H), 6.87 (d, 1H), 4.15 (t, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 2.77 (t, 2H), 2.35 (s, 6H).

III-086:

(*E*)- 3-(2,5-Dimethoxy-phenyl)-1-[4-(2-dimethylamino-ethoxy)-phenyl]-propenone



Fumarate

General procedure H gave the title compound as yellow crystals in 37% yield.

^{1}H NMR (DMSO-d_6) δ 8.15 (d, 2H), 8.00 (d, 1H), 7.89 (d, 1H), 7.54 (d, 1H), 7.07 (d, 2H), 7.04-7.01 (m, 2H), 6.57 (s, 2H), 4.26 (t, 2H), 3.84 (s, 3H), 380 (s, 3H), 2.92 (t, 2H), 2.41 (s, 6H).

Determination of metabolic stability

Incubations were performed with Wistar rat liver microsomes (0.5 mg/ml) in 2% sodium bicarbonate solution. NADP (0.15 mg/ml), glucose-6-phosphate (0.5 mg/ml) and glucose-6-phosophate dehydrogenase (0.38 units/ml) were used as NADPH generation system and UDPGA (0.48 mg/ml) was added to include the phase II reaction, glucuronic acid conjugation, in the assay. After 5 minutes of pre-incubation the reaction was started by addition of the test article to give a final concentration of 10µM. Samples were incubated for 30 min at 37°C and the reactions were terminated by addition of equal volumes of acetonitrile. Blank incubations were performed at the same concentration but without addition of microsomes.

The fraction of compound metabolised during the 30 min incubation was determined quantitatively by HPLC with UV detection using a Waters Alliance 2690 separation module and the Waters 996 PDA-detector, Waters corp. Milford, USA. Samples were analysed on a XTerra RP_8 column (5µm) 4.6 x 150 mm (Waters corp., Milford, USA) with a linear gradient elution system. Initial conditions were 40% mobile phase A (acetonitrile) and 60% mobile phase B (10mM ammonium acetate pH 9.5). During the first 20 minutes runtime, the mobile phase was changed to 90% A and 10% B followed by a fast 5 minutes gradient to return to initial conditions and a 5 minutes equilibration time. The flow rate was 1 ml/min and injection volume 50µl.

Determination of solubility

Solubility of the compounds was determined in 1M phosphate buffer pH 7.4 by preparation of suspensions in brown glass tubes. The suspensions were rotated slowly for 24 hours. Aliquots were centrifuged for 10 minutes at 10.000 rpm, supernatants were diluted in 50% acetonitrile prior to HPLC analysis and the concentrations in the samples were quantified against a standard curve. The concentration of the compound in the supernatant is used as term of solubility. The HPLC method used for the assessment of solubility is the same as used in the in vitro metabolism assay.

Biological testing

General methods

***In vitro* microbiological testing**

MIC determination in broth microdilution assay

Compounds were screened for activity against a panel of 10 different non-fastidious bacteria growing aerobically (*Staphylococcus aureus ATCC29213; Staphylococcus aureus ATCC33591;Staphylococcus intermedius #2357(clinical isolate from the Copenhagen area); Enterococcus faecalis ATCC29212;Enterococcus faecium #17501 (vancomycin-resistant clinical isolate); Streptococcus pneumoniae #998 (clinical isolate); Streptococcus pyogenes #14813 (clinical isolate); Streptococcus agalactiae #19855 (clinical isolate); Eschericia coli ATCC25922 and Eschericia coli ESS*). The screening assay was done in 200 µl MH-broth cultures in microtitre plates. For compounds exhibiting activity in the initial screen MIC was determined in a microdilution assay using MH-broth as described by *NCLLS* (National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – Fifth Edition. M7-A5 NCCLS 2000) modified to include uninoculated dilution series of test compounds to facilitate MIC determination if the test compound should precipitate. MIC was determined as the lowest concentration of test compound able to inhibit visible growth of bacteria. MICs for ATCC type strains fell within the limits posted by the *NCCLS* (National Committee for Clinical Laboratory Standards. Performance Stadards for Antimicrobial Susceptibility Testing; Eleventh Informational Supplement. M100-S11 NCCLS 2001) when tested against vancomycin, tetracycline, gentamycin.

MIC and MBC determination in broth macrodilution assay

MIC and MBC of test compounds were determined in a broth macrodilution assay using 2 ml MH-broth cultures and an inoculum of approximately 5x10E5 CFU/ml as described by Amsterdam (Amsterdam, D. Susceptibility testing of antimicrobials in liquid media. *In* V.Lorian (ed.): Antibiotics in Laboratory Medicin 4. edition. Williams & Wilkins 1996). MIC was determined as the minimal concentration of test compound able to inhibit visible growth of bacteria. Samples from cultures inhibited by test compound were plated onto unselective blood agar plates. MBC was determined as the minimal concentration of test compound able to decrease colony count on these plates below 0.1% compared to the original inoculum.

Killing Curve determination

For the determination of the killing curve of a test compound a dilution series of test compound was made and inoculated with approximately 5x10E5 CFU/ml as described for

the MIC macrodilution assay above. At the timepoints indicated 100 µl samples was withdrawn from the test tubes, serially diluted and spotted in duplicate on unselective agar plates to determine CFU. Test compounds with bactericidal activity is capable of decreasing surviving colony counts (CFU/ml) when incubated with bacteria. Bactericidal activity may be either primarily dependent on concentration of test compound or on incubation time with test compound. An example of a bactericidal compound (I-031), which is primarily dependent on the concentration of the test compound is shown in Figure 4. An example of a bactericidal compound (I-070) which is primarily dependent on the incubation time with the compound is shown in Figure 5.

MIC determination against Helicobacter pylori

Six strains of *Helicobacter pylori* were used in an agar dilution assay according to the standards of NCCLS (National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard - Fifth Edition. M7-A5 NCCLS 2000). MH-agar plates supplemented with 5% horse blood and containing a dilution series of the test compound were inoculated in duplicate with 10 µl spots of a 2 McF suspension of the different strains of *H.pylori*. This inoculum corresponds to approximately 10E6 CFU/spot. Plates were then incubated in a microaerophilic atmosphere at 35°C for 72 hours. The MIC endpoint was determined as the lowest concentration of test compound able to completely inhibit or most significantly reduce growth compared to growth control plates not containing test compounds.

Activity determination against anaerobic bacteria

Screening for activity against anaerobic bacteria was done against two isolates of *Bacteroides fragilis*, an isolate of *Clostridium difficile* and an isolate of *Clostridium perfringens* in an agar dilution assay as described by NCCLS (National Committee for Clinical Laboratory Standards. Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard - Fifth Edition. M11-A5 NCCLS 2000) with the exception that Mueller-Hinton agar was used in place of supplemented Brucella broth. Plates containing test compound at a single concentration (either 100 or 150 µM) were prepared in duplicate along with appropriate control plates. Activity was present if growth in the presence of test substance was absent or most significantly reduced compared to growth control plates not containg test compound.

Leishmania promastigote assay

A WHO reference vaccine strain of *L.major* originally isolated from a patient in Iran were cultured in Medium 199 with Hanks' Salts containing 0.02 mg/ml gentamycin, 25 mM HEPES, 4 mM L-glutamine, and 10% heat inactivated fetal calf serum (FCS). Incubation was carried out at 27°C. Promastigotes were harvested at day 3 of culture and used for the assay of inhibition of parasite growth.

The effect of test compounds on promastigotes was assessed by a method modified from Pearson et al. Briefly, promastigotes ($0.8x10^6$/well) were incubated in 200 µl duplicate cultures either with a dilution series of test compound or medium alone in 96 wells flat buttom microtiter plates. After 2h of incubation, 1.5 µCi of 3H-thymidine was added to each well and further incubated for 18 hours. The cultures were then harvested on Unifilter-GF/C microtiter filter plates (Packard Instruments), washed extensively and counted in a TopCount-NXT microplate scintillation counter (Packard Instruments).

Plasmodium falciparum assay

Plasmodium falciparum 3D7 was maintained in culture by a modification of the method originally described by Trager and Jensen. In brief, the parasites were grown in suspensions of human blood group 0 erythrocytes (RBC) maintained in RPMI1640 medium supplemented with 4.5 g/l Albumax II (Invitrogen), 10 mM hypoxantine, 1.4 mM L-glutamine and 0.05 mg/ml gentamicin. Cultures were incubated at 37°C in atmosphere of 92.5% nitrogen, 5.5% carbon dioxide, and 2% oxygen. To obtain synchronized cultures og parasites erythrocytes infected with late trophozoite and schizont stages were separated from ring stages and uninfected RBC by magnet-activated cell sorting (MACS; Miltenyi BioTec) (Staalsoe, T., H.A. Giha, D. Dodoo, T.G. Theander, and L. Hviid. 1999. Detection of antibodies to variant antigens on *Plasmodium falciparum*-infected erythrocytes by flow cytometry. Cytometry 35:329-336). Because of their high content of paramagnetic haemozoin, erythrocytes infected with late developmental stages of malaria parasites are specifically retained within the column. The column was washed with PBS supplemented with 2% foetal calf serum and then the column was removed from the magnet and the retained late developmental stages of parasites were eluted and cultured for an additional 18 hours. At this time the culture is highly synchronous containing more than 90% ring stages.

These synchronized cultures of ring stage parasites were used to assay for antimalarial parasites. Briefly, cultures of ring stage parasites were adjusted to 1% parasitemia by addition of uninfected RBC. Then, these were incubated in 125 µl duplicate cultures containing $2.5x10^7$ RBC/well with either a dilution series of test compound or with medium alone. Plates were then incubated at 37°C for 24 hours when cultures were labelled by the addition 1.1 µCi 3H-phenyalanine and incubated overnight. Then, the cultures were harvested on Unifilter-GF/C microfilter plates (Packard Instruments) and washed extensively with water followed by a wash with 10% H_2O_2 to bleach hemoglobin. Filter plates were counted in a TopCount-NXT microplate scintillation counter (Packard Instruments).

DHODH Assay

100 µl chalcone or 0.1 M Tris-HCl pH 8.0 is added to a well in a 96-wells microtiter plate. Then 50 µl enzyme dilution is added. The microtiter plate is placed in the Powerwave$_x$340 and the enzymatic reactions starts when adding 100 µl assay mixture. The reaction are

measured every 20 sec. for 10 min. The samples with chalcones are compared with the samples with 0.1 M Tris-HCl pH 8.0 and the percent inhibition is calculated.

Enzyme dilution: The solution of recombinant purified enzyme is dissolved in 0.1 M Tris-HCl pH 8 to give an initial velocity of 0.04 - 0.05 ΔA/min.

2,6-dichlorophenolindophenol (DCIP)-stock solution: 40 mg DCIP and 10 ml 99 % Ethanol are mixed for 10 min at RT. Then 100 µl 1.0 M Tris-HCl pH 8 and miliQ H_20 are added to a final volume of 100 ml. The A_{600} of the DCIP-stock solution are measured in a microtiter plate on the Powerwave$_x$340 (Bio-Tek instruments,Inc.)

Dihydroorotate dehydrogenase (DHODH)-stock solution: 25 mM dihydroorotate stock-solution is prepared by first dissolving in the same amount of mol NaOH and then miliQ H_20 is added to the final volume.

Assay mix (10 ml solution): 600 µl of DHODH-stock solution and X ml (depending on the A_{600} value of stock-solution) DCIP to a final A_{600} = 2.5 are mixed. Then 0.1 M Tris-HCl pH 8.0 are added to a final volume of 10 ml.

Preparation of compound soluton: A 10 mM stock-solution of compound (e.g. a chalcone derivative) is made in dimethylsulfoxid (DMSO). The compound is then diluted in 0.1 M Tris-HCl pH 8 to the test concentrations. The final DMSO concentration in the sample is 10%

Biological Results

Licochalcone A (LicA) and 4'methoxy chalcone (4'MC) described in WO 93/17671 are used as reference compounds in the following discussion.

Activity against non-fastidious bacteria

Licochalcone A exhibit moderate bactericidal activity against common pathogenic Gram-positive non-fastidious bacteria including *Staphylococcus aureus, Enterococcus faecalis, Enterococcus faecium, Streptococcus pneumoniae, Streptococcus pyogenes,* and *Streptococcus agalactiae*. Licochalcone A maintains its activity also against antibiotic resistant bacteria, e.g. *Staphylococcus aureus ATCC33591* (resistant to methicillin) and *Enterococcus faecium #17051* (resistant to vancomycin). In contrast, Licochalcone A have only modest or no activity against the prototype pathogenic Gram-negative bacterium, *Eschericia coli.* 4'MC as a representative of non-hydroxyl chalcones exhibit no antibacterial effect at all.

In comparison with Licochalcone A, aminoalkoxy-functional chalcones retain the activity of Licochalcone A against pathogenic Gram-positive bacteria including antibiotic-resistant strains (cf. Table SS). The aminoalkoxy-functional chalcones exhibit increased potency against Gram-positive pathogens (e.g. III-025, III-036, III-044, III-051, III-058, III-064).

In contrast to Licochalcone A, aminoalkoxy-functional chalcones exhibit activity against *Eschericia coli*. Thus, several aminoalkoxy-functional chalcones (e.g. III-025, III-051, III-053, III-055, III-056, III-058, III-060) obtain MICs on 75 µM against *E.coli ATCC25922* and on 9.4-18.8 µM against the general more susceptible ESS strain of *E.coli*. This indicates the potential use of aminoalkoxy-functional chalcones in the treatment of infections with Gram-negative bacteria.

In the treatment of severe infections in immunocompromised patients bactericidal action of a antibiotic is a necessity. As exemplified in Figures 2 and 3, aminoalkoxychalcones retain the bactericidal action of Licochalcone A. For aminoalkoxychalcones the bactericidal action is predominantly dependent on the concentration of the compound (e.g. III-044 and III-051; cf. Figure 2 and 3). This knowledge is helpful when designing dosing regimens for *in vivo* efficacy trials.

Tabel SS. Comparison of the effect of aminoalkoxy-chalcones and Licochalcone/4'MC on bacteria; MIC values in µM.

	A	B	C	D	E	F	G	H
LICA	**37.5**	**37.5**	**37.5**	**37.5**	**37.5**	**75.0**		**300.0**
4'-MC	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**
III-025	9.4	9.4	18.8	18.8	18.8	18.8	75.0	9.4
III-034	4.7	4.7	9.4	9.4	9.4	18.8		4.7
III-036	9.4	9.4	9.4	9.4	9.4	37.5		9.4
III-044	4.7	4.7	4.7	4.7	4.7	18.8		9.4
III-049	9.4	18.8	18.8	18.8	9.4	37.5		9.4
III-051	9.4	9.4	18.8	4.7	4.7	2.4	75.0	9.4
III-058	18.8	18.8	18.8	18.8	18.8	18.8	37.5	18.8
III-060	9.4	18.8	18.8	18.8	18.8	18.8	75.0	9.4
III-061	18.8	18.8	18.8	37.5	37.5	37.5		18.8
III-064	18.8	37.5	18.8	37.5	18.8	18.8		18.8

***A**:Staphylococcus aureus ATCC29213; **B**:Staphylococcus aureus ATCC33591; **C**: Staphylococcus intermedius #2357(clinical isolate from the Copenhagen area); **D**: Enterococcus faecalis ATCC29212; **E**: Enterococcus faecium #17501 (vancomycin-resistant clinical isolate); **F**: Streptococcus pneumoniae #998 (clinical isolate); **G**: Eschericia coli ATCC25922 and **H**: Eschericia coli ESS*. NA: no activity.

Activity against Helicobacter pylori

Colonisation of the gastric mucosa with *Helicobacter pylori* is an important pathogenic determinant for the development of gastritis and peptic ulcer. Aminoalkoxychalcones exhibit activity against *Helicobacter pylori*. Several aminoalkoxychalcones (e.g.III-025, III-031, III-035, III-043, III-051) exhibit MICs in the range between 12 µM and 25 µM when tested against a panel of six strains *Helicobacter pylori*, that includes strains resistant to metronidazole. Metronidazol is an antibiotic commonly included in treatment regimens designed to eradicate *Helicobacter* colonization for the treatment of peptic ulcer. The

activity of aminoalkoxychalcones against both metronidazole-resistant and sensitive *Helicobacter pylori* clearly indicates the potential use of these compounds in the treatment of *Helicobacter* infections.

Activity against anaerobic bacteria

Aminoalkoxychalcones have been assayed in a single concentration of compound (100 μM) for activity against a panel of anaerobic bacteria containing common human pathogenic bacteria (*Bacteroides fragilis, Clostridium perfringens, Clostridium difficele*). Several aminoalkoxychalcones (e.g. III-036, III-046, III-047, III-049 and III-064) exhibit activity against all microorganisms within the test panel. This clearly indicates the potential use of aminoalkoxychalcones in treatment of infection caused by anaerobic bacteria.

Activity against protozoa

Activity against Leishmania major

Leishmania major is a protozoan parasite transmitted by the sandfly, *Phlebotomus*, and causing cutaneous leishmaniasis or kala-azar in humans. Licochalcone A exhibit activity against *Leishmania* parasites and has shown efficacy in experimental animal models of cutaneous and visceral *Leishmania* infection (Chen et al., 1994). Aminoalkoxychalcones exhibit activity *in vitro* against *Leishmania major* with significantly improved potency compared to Licochalcone A and 4'MC (cf. Table WW). The results clearly indicate the potential use of aminoalkoxychalcones in the treatment of *Leishmania* infection.

Table WW. Effect of aminoalkoxy-chalcones on *L. major*.

Comp.	IC_{50} in μM
LICA	5.0
4'MC	5.6
III-025	0.2
III-032	0.1
III-036	0.1
III-041	0.03
III-045	0.04
III-053	0.7
III-058	0.5
III-064	0.2

Activity against Plasmodium falciparum

Plasmodium falciparum is a protozoan parasite transmitted by the mosquito, *Anopheles*, and causing malignant or severe malaria in humans. Licochalcone A exhibit activity against *Plasmodium falciparum in vitro* and protects mice from infection with *P.yoelii* and *P.berghei*

(Chen et al., 1994). Aminoalkoxychalcones exhibit activity *in vitro* against *Plasmodium falciparum* and several aminoalkoxychalcones exhibit improved potency compared to Licochalcone A (cf. Table TT and Figure 4). The results clearly indicate the potential use of aminoalkoxychalcones in the treatment of malaria.

Table TT Activity against *Plasmodium falciparum 3D7.*

Comp.	IC_{50} in µM
LICA	5.9
4'MC	40.0
III-025	1.9
III-047	1.3
III-051	0.6
III-052	0.9
III-053	0.5
III-056	0.1
III-057	0.2
III-058	1.0
III-059	0.2

Metabolism

The usefulness of chalcones as drug candidates have been limited by the metabolism of the compounds resulting in short half-lives *in vivo* (Lica: 100% turn-over *in vitro* and $t_{½}$= 10 min *in vivo*).

The introduction of a aminoalkoxy group in the chalcone changes the metabolic properties; this is clear from Table QQ where the metabolic turn-over of a number of aminoalkoxy-chalcones are compared to LicA. The aminoalkoxy-chalcones prepared are expected to show low or no metabolism *in vivo* as the metabolic turn-over are between 0-20% (compared to 100% turn-over for Lica). Consequently the half-life of a aminoalkoxy-chalcone will be longer, reducing the dose needed for treatment.

Table QQ. Metabolic turn-over in vitro (%).

LICA	**100.0**
III-022	0.0
III-023	15.9
III-067	0.0
III-069	0.0
III-070	1.7
III-078	0.0
III-086	0.8

Inhibition of DHODH

Several of the aminoalkoxy-chalcones prepared are potent inhibitors of DHODH. The compounds are as potent as LicA and by far more potent than ordinary chalcones exemplified by 4'MC.

Table DD. Inhibition of DHODH at 10 μM.

Comp.	Inhibition (%)
LICA	**24.5**
4'MC	**7.0**
III-040	18.0
III-041	18.0
III-043	20.5
III-047	18.5
III-048	21.5
III-049	22.5

Solubility

The solubility of the neutral chalcones descibed in WO 93/17671 was very low. A representative chalcone 4'-methoxy-chalcone has a solubility <0.05 mg/ml. A few chalcones have a higher solubility due to (metabolically unstable) hydroxyl groups in the molecule. LicA has a solubility of 0.2 mg/ml.

The aminoalkoxy-chalcones described in this application are superior having solubility numbers in sub-mg/ml. Representative examples are

III-056: 0.6 mg/ml
IIII-070: 0.8 mg/ml

The high solubility means that dissolution and hence absorption will be no problem. This will inevitably cause a dramatic reduction of the dose needed making the aminoalkoxy-chalcones very usefull as drug candidates.

Conclusion

The use of chalcones as drug candidates for the treatment of parasitic or bacterial infections have been limited by the low in vivo potency (50mg/kg for LicA) of the compounds and a narrow spectrum of activity.

Several factors contribute to the low in vivo potency: Fast metabolism resulting in short half-lives in vivo; Low/no solubility in the intestine and consequently low/no absorption; Medium potency of the compounds against parasites and no activity against bacteria (except for LicA).

The aminoalkoxy-chalcones in this application are expected to fulfill the criteria for a drug candidate. The metabolism is low, the solubility is high and the compounds are potent against parasites as well as (resistant) Gram positive and Gram negative bacteria.

CLAIMS

1. A compound of the general formula

$$Y^1(X^1)\text{-}Ar^1\text{-}C(=O)\text{-}V\text{-}Ar^2(X^2)Y^2$$

wherein Ar^1 and Ar^2 independently are selected from aromatic rings (aryl) and heteroaromatic rings (heteroaryl);

V designates $-CH_2-CH_2-$, $-CH=CH-$ or $-C\equiv C-$, preferably $-CH=CH-$;

at least Y^2 of Y^1 and Y^2 represent at least one, such as 1-2, e.g. one, aminoalkoxy-functional substituent(s) of the formula

$$-O-Z-N(R^1)R^2$$

wherein Z is a biradical $-(C(R^H)_2)_n-$, wherein n is an integer in the range of 1-6, preferably 2-4, such as 2-3, and each R^H is independently selected from hydrogen and C_{1-6}-alkyl;

R^1 and R^2 independently are selected from hydrogen, optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{4-12}-alkadienyl, optionally substituted C_{6-12}-alkatrienyl, optionally substituted C_{2-12}-alkynyl, optionally substituted C_{1-12}-alkoxycarbonyl, optionally substituted C_{1-12}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted arylcarbonyl, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl; or R^1 and R^2 together with the nitrogen atom to which they are attached ($-N(R^1)R^2$) form an optionally substituted nitrogen-containing heterocyclic ring;

X^1 designates 0-5, preferably 0-4, such as 0-3, e.g. 0-2, substituents, and X^2 designates 1-5, preferably 1-4, such as 1-3, e.g. 1-2 substituents, where such substituents independently are selected from optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{4-12}-alkadienyl, optionally substituted C_{6-12}-alkatrienyl, optionally substituted C_{2-12}-alkynyl, hydroxy, optionally substituted C_{1-12}-alkoxy, optionally substituted C_{2-12}-alkenyloxy, carboxy, optionally substituted C_{1-12}-alkoxycarbonyl, optionally substituted C_{1-12}-alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroaryloxycarbonyl, optionally substituted heteroaryloxy, optionally substituted heteroarylcarbonyl, optionally substituted heteroarylamino, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally

substituted heterocyclyloxycarbonyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylcarbonyl, optionally substituted heterocyclylamino, heterocyclylsulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkyl-carbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, amino-C_{1-6}-alkyl-amino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-amino, cyano, guanidino, carbamido, C_{1-6}-alkanoyloxy, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyloxy, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, nitro, optionally substituted C_{1-6}-alkylthio, and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, C_{2-6}-alkenyloxy, amino, mono- and di(C_{1-6}-alkyl)amino, carboxy, C_{1-6}-alkylcarbonylamino, halogen, C_{1-6}-alkylthio, C_{1-6}-alkyl-sulphonyl-amino, or guanidine;

and salts thereof.

2. The compound according to claim 1, wherein R^1 and R^2 independently are selected from hydrogen, optionally substituted C_{1-12}-alkyl, optionally substituted C_{2-12}-alkenyl, optionally substituted C_{2-12}-alkynyl, optionally substituted C_{1-12}-alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, and mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl.

3. The compound according to any of the preceding claims, wherein X^1 designates 0-4, such as 0-3, e.g. 0-2, substituents, and X^2 designates 1-4, such as 1-3, e.g. 1-2, substituents, where such optional substituents independently are selected from optionally substituted C_{1-12}-alkyl, hydroxy, optionally substituted C_{1-12}-alkoxy, optionally substituted C_{2-12}-alkenyloxy, carboxy, optionally substituted C_{1-12}-alkylcarbonyl, formyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxycarbonyl, optionally substituted aryloxy, optionally substituted arylcarbonyl, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, optionally substituted heteroarylcarbonyl, optionally substituted heteroaryloxy, heteroarylsulphonylamino, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkyl-carbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, amino-C_{1-6}-alkyl-amino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-amino, guanidino, carbamido, C_{1-6}-alkylsulphonyl, C_{1-6}-alkylsulphinyl, C_{1-6}-alkylsulphonyloxy, optionally substituted C_{1-6}-alkylthio, aminosulfonyl, mono- and di(C_{1-6}-alkyl)aminosulfonyl, and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, and/or halogen.

4. The compound according to any of the preceding claims, wherein R^1 and R^2 independently are selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{1-6}-alkylcarbonyl, heteroarylcarbonyl, aminocarbonyl, mono- and di(C_{1-6}-

alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl

5. The compound according to any of the preceding claims, wherein X^1 designates 0-3, e.g. 0-2, substituents, and X^2 designates 1-3, e.g. 1-2, substituents, where such optional substituents independently are selected from optionally substituted C_{1-6}-alkyl, hydroxy, optionally substituted C_{1-6}-alkoxy, carboxy, optionally substituted C_{1-6}-alkylcarbonyl, C_{1-6}-alkylsulphonylamino, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, arylsulphonylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, heteroarylsulphonylamino, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, C_{1-6}-alkylcarbonylamino, amino-C_{1-6}-alkyl-carbonylamino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-carbonylamino, amino-C_{1-6}-alkyl-amino, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-amino, guanidino, carbamido, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen, where any nitrogen-bound C_{1-6}-alkyl may be substituted with hydroxy, C_{1-6}-alkoxy, and/or halogen.

6. The compound according to any of the preceding claims, wherein V designates -CH=CH-.

7. The compound according to any of the preceding claims, wherein at least one of Ar^1 and Ar^2, preferably both, are aromatic rings, in particular phenyl rings.

8. The compound according to claim 8, wherein both of Ar^1 and Ar^2 are phenyl rings and Y^2 represents at least one aminoalkoxy-functional substituent, one of which being located in the 2-position of the phenyl ring, and X^2 represents at least one substituent, one of which being located in the 5-position of the phenyl ring.

9. The compound according to any of the preceding claims, wherein X^2 represents at least one substituent selected from C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy, C_{1-6}-alkylcarbonyl, optionally substituted aryl, optionally substituted aryloxy, optionally substituted arylamino, optionally substituted heteroaryl, optionally substituted heteroarylamino, mono- and di(C_{1-6}-alkyl)amino, C_{1-6}-alkylcarbonylamino, optionally substituted C_{1-6}-alkylthio, optionally substituted heterocyclyl, optionally substituted heterocyclyloxy, optionally substituted heterocyclylamino and halogen, in particular from C_{1-6}-alkyl, optionally substituted phenyl, and hydroxy, e.g. from C_{1-6}-alkyl and optionally substituted phenyl.

10. The compound according to any of the preceding claims, wherein both of Ar^1 and Ar^2 are phenyl rings, and X^1 represents at least one substituent, one of which being located in the 2- or 3-position of the phenyl ring, and preferably being selected from amino-C_{1-6}-alkyl and mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl.

11. The compound according to any of the preceding claims, wherein both of Ar^1 and Ar^2 are phenyl rings, and X^1 represents at least one substituent, one of which being located in

the 4-position of the phenyl ring, and preferably being selected from hydroxy, amino-C_{1-6}-alkylamino and mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkylamino.

12. The compound according to any of the preceding claims, wherein at least one or Ar^1 and Ar^2 is selected from thiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, thiophenyl, quinolyl, isoquinolyl, and indolyl.

13. The compound according to any of the preceding claims, wherein Z is $-(CH_2)_n-$ wherein n is 2-4, such as 2-3.

14. The compound according to any of the preceding claims, wherein one of Y^1 and Y^2 represent a substituent of the formula

$$-O-(CH_2)_{2-3}-N(R^1)R^2$$

wherein R^1 and R^2 is selected from hydrogen and C_{1-6}-alkyl.

15. A compound according to claim 14, wherein V is -CH=CH-, and Ar^1 and Ar^2 both are phenyl rings.

16. A pharmaceutical composition comprising a compound as defined in any of the claims 1-15 in combination with a pharmaceutically acceptable carrier.

17. A compound as defined in any of claims 1-15 for use as a drug substance.

18. The use of a compound as defined in any of the claims 1-15 for the preparation of a pharmaceutical composition for the treatment of bacterial infections in a mammal in need thereof.

19. The use according to claim 18, wherein the bacterial infection is caused by a bacteria selected from Gram-positive bacteria, Gram-negative bacteria, microaerophilic bacteria, and anerobic bacteria.

20. The use according to claim 19, wherein the bacteria is a microaerophilic bacteria, e.g. a bacteria associated with gastric disease, such as *Helicobacter pylori*.

21. The use according to claim 19, wherein the bacteria is selected from antibiotic-sensitive and -resistant strains of *S.aureus*.

22. The use according to claim 19, wherein the bacteria is selected from antibiotic-sensitive and -resistant strains of *E.faecium*.

23. The use according to claim 19, wherein the bacteria is selected from a *S.pneumoniae* and *S.pyogenes*.

24. The use according to claim 19, wherein the bacteria is a member of *Enterobacteriaceae*, e.g. E.coli.

25. The use according to claim 19, wherein the bacteria is a pathogenic anaerobic bacteria, e.g. *Bacteroides fragilis* or *Clostridium species*.

26. The use of a compound as defined in any of claims 1-15, for the preparation of a pharmaceutical composition for the treatment of infections caused by protozoa in a mammal.

27. The use according to claim 26, wherein the infection is caused by a protozoa selected from *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae*.

28. The use of a compound as defined in any of the claims 1-15, for the preparation of a pharmaceutical composition for the treatment of infections in a mammal caused by *Leishmania spp.*

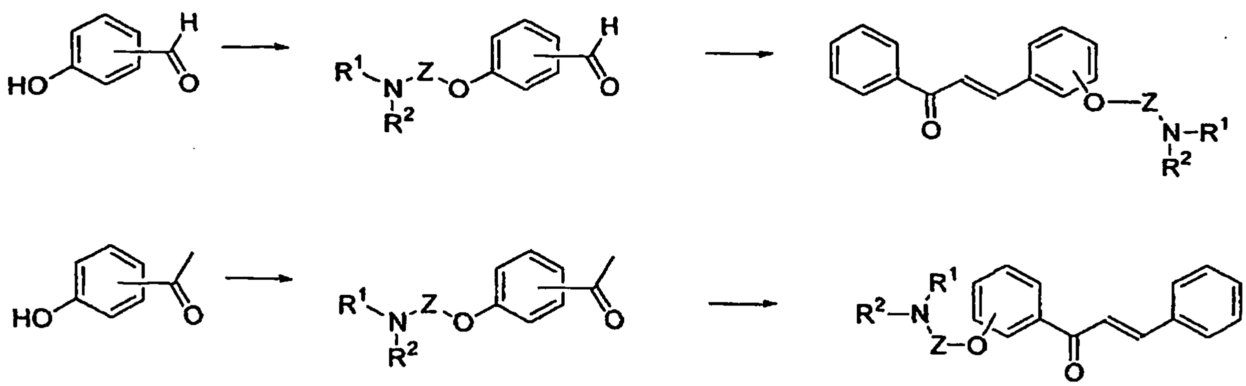
29. The use according to claim 28, wherein the infection is cutaneous and/or visceral.

30. A method of predicting whether a chemical compound has a potential inhibitory effect against a microorganism selected from *Helicobacter pylori* and *Plasmodium falciparum*, said method comprising preparing a mixture of a dihydroorotate dehydrogenase, a substrate for dihydroorotate dehydrogenase and the chemcial compound, measuring the enzymatic activity of dihydroorotate dehydrogenase (A), comparing the enzymatic activity of dihydroorotate dehydrogenase (A) with the standard activity of dihydroorotate dehydrogenase (B) corresponding to the activity of a dihydroorotate dehydrogenase in a similar sample, but without the chemical compound, predicting that the chemical compound has a potential inhibitory effect against *Helicobacter pylori* and *Plasmodium falciparum* if A is significantly lower than B.

31. The method according to claim 30, wherein the chemical compound is a chalcone derivative.

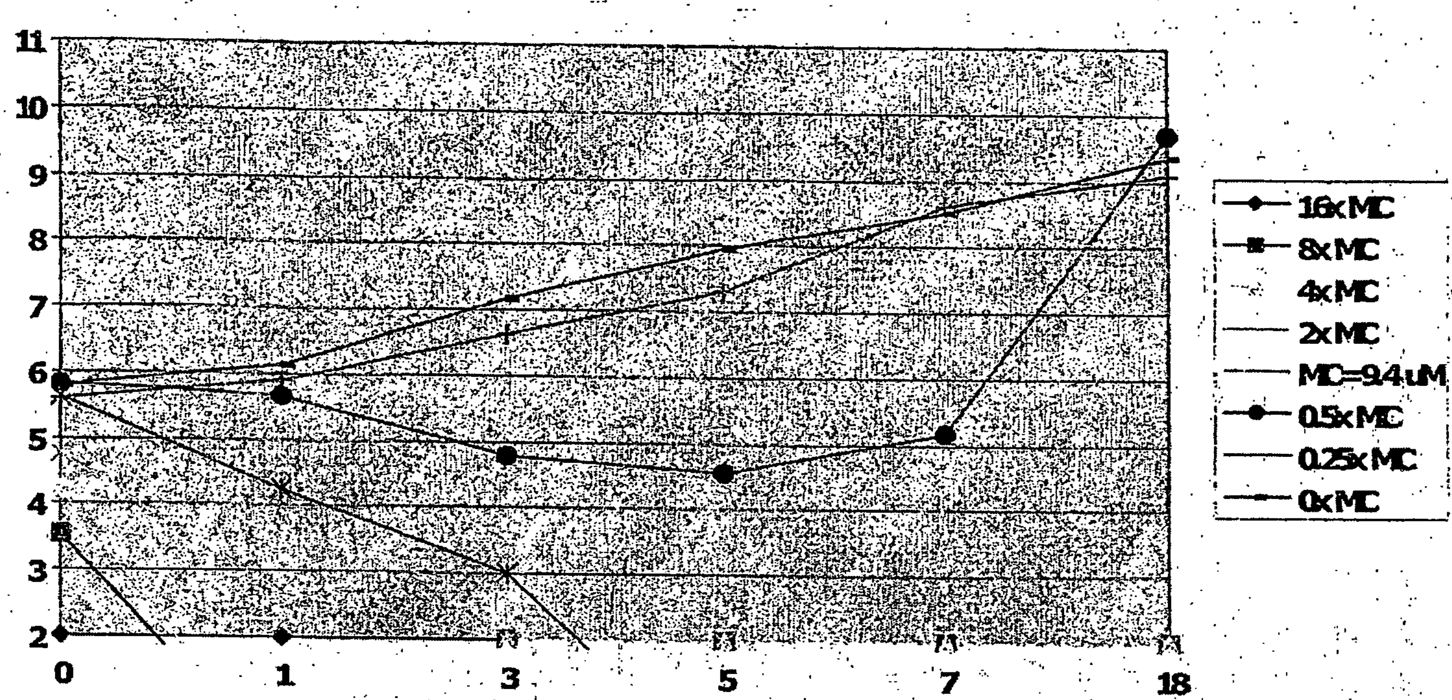
32. The method according to claim 30, wherein the chemical compound is a chalcone derivative as defined in any of the claims 1-15.

Figure 1



igure 2

III-044 (SA33591)



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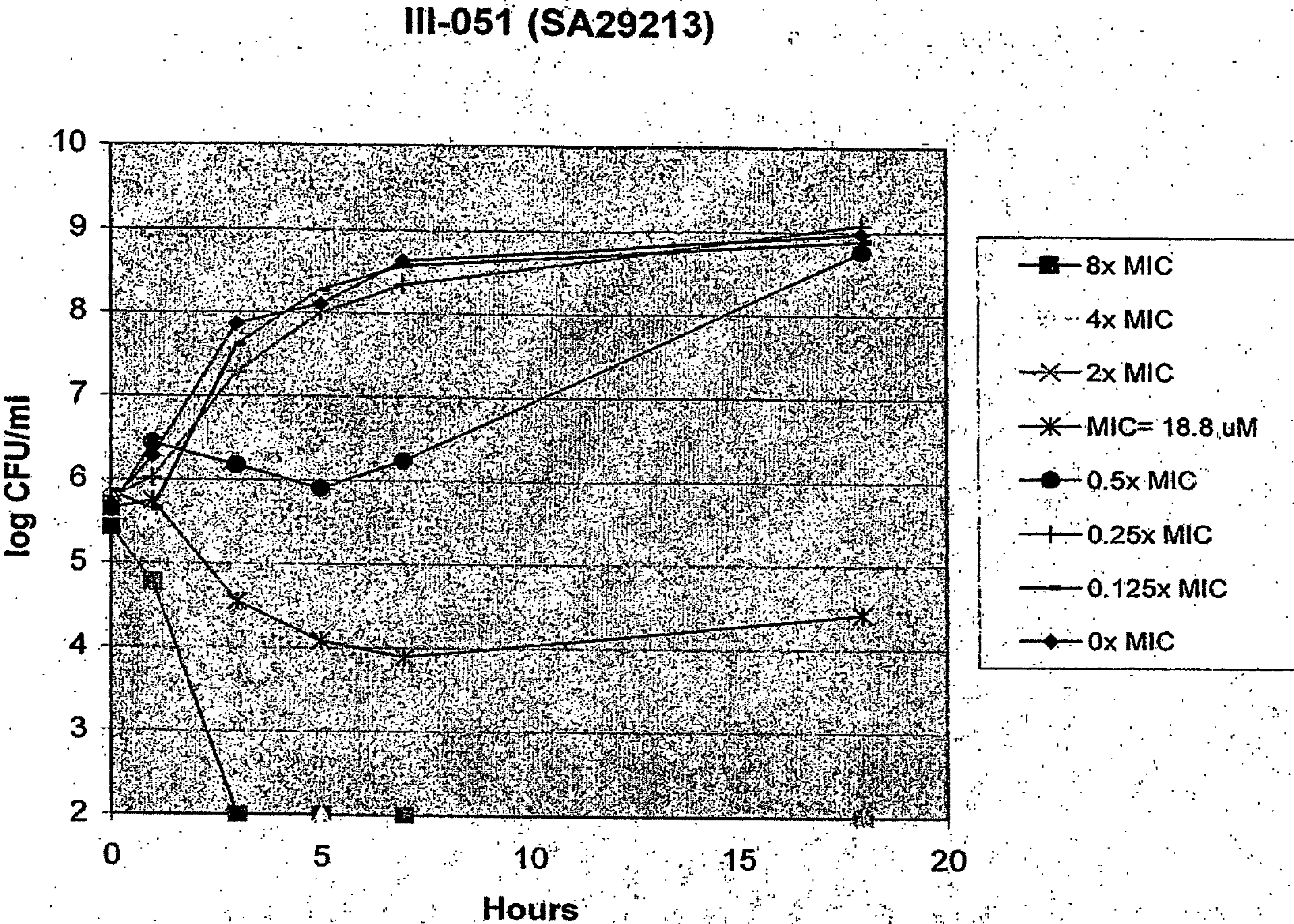
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7
6
5
4
3
2
0
5
10
15
20
Hours
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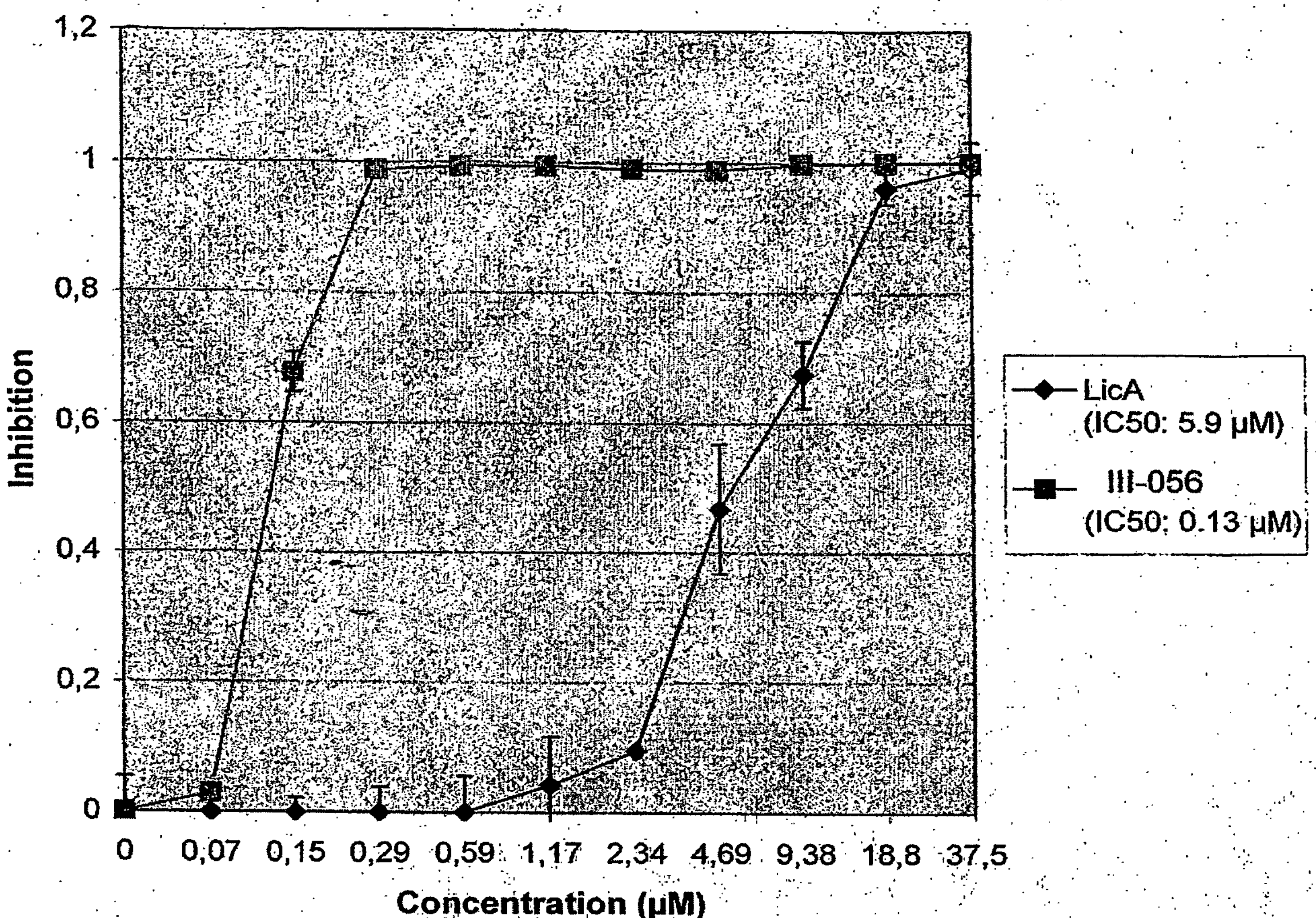
4x MIC
2x MIC
MIC= 18.8 uM
0.5x MIC
0.25x MIC
0.125x MIC
0x MIC

Figure 4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Concentration (µM)
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(IC50: 5.9 µM)
III-056
(IC50: 0.13 µM)